UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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In re:

REZULIN PRODUCTS LIABILITY LITIGATION — MDL No. 1348

This document relates to: All Cases. — Master File 00 Civ. 2843 (LAK)

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OPINION

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LEWIS A. KAPLAN, *District Judge*.

In 1996, Warner-Lambert Company ("Warner-Lambert"), now owned by Pfizer Inc., announced the development of Rezulin, the trade name of a drug used to treat Type 2 diabetes, a disease affecting approximately 16 million Americans.[1] The United States Food and Drug Administration approved the drug in 1997, and it was administered to 1.92 million people. Following reports that some patients taking Rezulin experienced liver failure resulting in transplant or death, the drug was withdrawn from the market in March 2000.[2] This led to the commencement of thousands of lawsuits for alleged personal injuries or apprehension of personal injuries in consequence of the ingestion of the drug.[3] The federal actions have been consolidated in this Court for pretrial proceedings.[4]

Extensive liability discovery against defendants has been completed. Defendants Pfizer Inc., Warner-Lambert, and Parke-Davis[5] (collectively, "Pfizer") move, pursuant to Federal

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1 *See* Edwin A.M. Gale, *Lessons from the Glitazones: A Story of Drug Development*, 357 LANCET 1870, 1870-01 (2001) (Ex. 69); Paul Angulo, *Nonalcoholic Fatty Liver Disease*, 346 N. ENG. J. MED. 1221, 1222 (2002) (Ex. 5); CENTERS FOR DISEASE CONTROL AND PREVENTION, DIABETES: A SERIOUS PUBLIC HEALTH PROBLEM 2 (2000) (Ex. 349).

2 *See* Gale, *supra*, at 1870-01; Chojkier Report 2 (Ex. 319).

3 In general, plaintiffs sue on theories of negligence, strict products liability, breach of express and implied warranties, fraud, and misrepresentation. Defendants include Pfizer, and, in many cases, drug company sales representatives, pharmacies, pharmacists, and physicians. Plaintiffs claim that their alleged liver injuries were caused or exacerbated by Rezulin.

4 The Court denied plaintiffs' motion for class certification in September 2002. *In re Rezulin Prods. Liab. Litig.*, 210 F.R.D. 61 (S.D.N.Y. 2002), *recons. denied*, 224 F.R.D. 346 (S.D.N.Y. 2004).

5 Parke-Davis was an unincorporated division of Warner-Lambert that produced the drug.

Rule of Evidence 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*,[6] to exclude "proposed expert testimony that Rezulin can cause a liver injury, or exacerbate a pre-existing liver condition, in the absence of marked elevation of liver enzymes while the patient was taking the medication."[7] The Plaintiffs' Executive Committee, which is responsible for coordinating the activities of plaintiffs during pretrial proceedings,[8] retained the experts and is defending this motion.

I. The Legal Backdrop and the Positions of the Parties

Causation in toxic tort cases has two components, general and specific, and the plaintiff must establish both in order to prevail.[9] "General causation is whether a substance is

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6 509 U.S. 579 (1993).

7 Mot.

For purposes of this motion, marked elevation of enzymes refers to an increase of the concentration in the blood of alanine aminotransferase ("ALT"), aspartate aminotransferase ("AST"), alkaline phosphatase, or bilirubin to more than twice the upper limit of the normal range. *See* Def. Mem. 1 n.1, 8 n.10; Def. Reply Mem. 21, 27-28; Tr. 4/23/03, at 88, 106; Tr. 5/21/03, at 248. The Court is aware that bilirubin – "a chemical derived from the break down of old red blood cells," Watkins (5/3/01) Decl. ¶ 5 (Ex. 330) – is not an enzyme. *See generally* Jayanta Roy Chowdhury et al., *Bilirubin Metabolism and Its Disorders*, *in* 1 HEPATOLOGY: A TEXTBOOK OF LIVER DISEASE 233 (David Zakim & Thomas D. Boyer eds., 4th ed. 2003) (hereinafter HEPATOLOGY: A TEXTBOOK OF LIVER DISEASE). The Court nonetheless includes bilirubin in that category for convenience of expression.

The defendants define "while the patient was taking the medication" as up to 15 days after the patient stopped taking Rezulin (for purposes of hepatocellular injury) and up to one month after the patient stopped taking Rezulin (for purposes of cholestatic or mixed injury). Def. Reply Mem. 21 & n.17. For the definitions of hepatocellular, cholestatic, and mixed injury, see section III.B. below.

8 *See* Pretrial Order No. 1.

9 *See, e.g.*, *In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1129 (9th Cir. 2002); *Bonner v. ISP Techs., Inc.*, 259 F.3d 924, 928 (8th Cir. 2001); *Raynor v. Merrell Pharms, Inc.*, 104 F.3d 1371, 1376 (D.C. Cir. 1997); *Sterling v. Velsicol Chem. Corp.*, 855 F.2d 1188,

capable of causing a particular injury or condition in the general population, while specific causation is whether a substance caused a particular individual's injury."[10] As explained in the Federal Judicial Center's *Reference Manual on Scientific Evidence*:

> "General causation is established by demonstrating, often through a review of scientific and medical literature, that exposure to a substance can cause a particular disease (e.g., that smoking cigarettes can cause lung cancer). Specific, or individual, causation, however, is established by demonstrating that a given exposure is the cause of an individual's disease (e.g., that a specific plaintiff's lung cancer was caused by his smoking)."[11]

Plaintiffs offer the testimony of a number of expert witnesses to prove general causation. As relevant here, they would opine that Rezulin is capable of causing liver injury "silently," that is without markedly elevating liver enzymes, and that such injury is a consequence of a form of liver cell death, known as apoptosis, that the experts assert can be induced by Rezulin.

Pfizer contends that plaintiffs' experts' testimony is insufficiently reliable to satisfy *Daubert* and Rule 702. It claims that their theories are unsupported by testing and that the potential rate of error therefore cannot be determined. They maintain also that they have not been subjected to peer review and publication and that they do not have widespread acceptance in the scientific community. Furthermore, Pfizer argues that the opinions of plaintiffs' experts are not the product of independent research but were developed solely for this litigation and, finally, that the experts overlook or ignore contrary evidence. The plaintiffs resist these assertions.

1200 (6th Cir. 1988).

10 *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1224 (D. Colo. 1998).

11 Mary Sue Henifin, Howard M. Kipen & Susan R. Poulter, *Reference Guide on Medical Testimony*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 439, 444 (Fed. Jud. Ctr., 2d ed. 2000) (hereinafter *Reference Guide on Medical Testimony*).

II. Proceedings on the Motion

Each side has submitted thousands of pages of expert reports, scientific and medical articles, depositions and other documents in connection with the motion. The Court heard oral argument and then conducted a two-day evidentiary hearing at which three of the plaintiffs' experts and one defense expert testified.[12] The Court then had the benefit of extensive proposed findings of fact from each side and point-by-point responses to each set of proposed findings.

III. Scientific Background

A. Relevant Physiology

1. Cells

The human body consists of cells. The cell has three basic components: the nucleus, the cytoplasm, and the plasma membrane.[13] The nucleus contains the cell's genetic information.[14] The plasma membrane surrounds the cell and "acts as a selective barrier that enables the cell to concentrate nutrients gathered from its environment and retain the products it synthesizes for its own use, while excreting waste products."[15] The cytoplasm is defined as everything besides the nucleus

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12 *See* Tr. 4/23/03, at 118-19. The plaintiffs' experts who testified were Drs. Smith, Reed, and Julie. See section IV.A. below. Dr. Mario Chojkier testified for the defendants.

At the conclusion of these proceedings, the Court requested the parties to prepare a joint list of all matters in the record. Tr. 5/21/03, at 375-76. All exhibit references used in this opinion correspond to this joint index.

13 *See* BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL G:10 (4th ed. 2002).

14 *Id.* at G:25.

15 *Id.* at 11.

and cell membrane,[16] and it contains among other things membrane-bound structures known as organelles, of which one type is the mitochondrion (in the plural, mitochondria).[17] The mitochondria sometimes are referred to as the "powerhouse" of the cell[18] because chemical reactions occurring therein produce adenosine triphosphate ("ATP"), the cell's energy currency.[19]

2. The Liver

The liver, located in the right upper quadrant of the abdomen, is a large organ that plays a central role in the body's biochemical activity. It metabolizes, or breaks down, a large number of substances, synthesizes essential enzymes, and detoxifies and eliminates a variety of compounds from both within and without the liver.[20] A vein known as the portal vein carries to the liver all blood from the digestive tract, facilitating the liver's absorption of toxic chemicals that a person has ingested.[21] Most of the liver's biochemical functions take place within cells known as

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16 *Id*. at G:10.

17 *Id*. at G:22, G:25.

18 *See, e.g.*, Day Decl. ¶ 24 (Ex. 334).

19 *E.g.*, Alberts et al., *supra*, at 767-781.

20 *See* Watkins (5/3/01) Decl. ¶ 5 (Ex. 330); Romil Saxena et al., *Anatomy and Physiology of the Liver*, *in* 1 HEPATOLOGY: A TEXTBOOK OF LIVER DISEASE, *supra*, at 3, 3.

21 *See* Saxena et al., *supra*, at 3; Mary Treinen-Moslen, *Toxic Responses of the Liver*, *in* CASARETT AND DOULL'S TOXICOLOGY 479 (Curtis D. Klaassen ed., 6th ed. 2001) (hereinafter CASARETT AND DOULL'S).

hepatocytes, which are the predominant type of cell in the liver.[22]

Medicine recognizes many forms of liver disease, including non-alcoholic fatty liver disease ("NAFLD"), described as "fatty liver without inflammation,"[23] and a related condition[24] known as non-alcoholic steatohepatitis ("NASH"), described as "fatty liver with inflammation."[25] These conditions are associated with fibrosis,[26] described as "scarring of the liver"[27] and more precisely as "the presence of excess extracellular matrix."[28] Fibrosis can lead to cirrhosis,[29] a final

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22 Watkins (5/3/01) Decl. ¶ 5 (Ex. 330).

23 Maddrey Report ¶ 4 (Ex. 326).

24 Physicians do not always distinguish clearly between NAFLD and NASH. *See* Maddrey (11/1/02) Dep. 120 (Ex. 291) ("And I must tell you, nonalcoholic fatty liver disease and nonalcohol steatohepatitis are so much on overlap, most of us use one or the other. . . . It's not a fine line, really, between all of those things."). NAFLD, according to one textbook, "compris[es] a spectrum of morphologic changes associated with fatty liver in the non-alcoholic," of which one is steatohepatitis. Jay H. Lefkowitch, *Histopathologic Diagnosis of Liver Disease*, *in* 1 HEPATOLOGY: A TEXTBOOK OF LIVER DISEASE, *supra*, at 721, 725.

25 Maddrey Report ¶ 4 (Ex. 326).

26 *See* Kaplowitz Report ¶¶ 15, 36 (Ex. 323); Paul Angulo, *Nonalcoholic Fatty Liver Disease*, 346 N. ENG. J. MED. 1221, 1223 (2002) (Ex. 5) ("According to a number of cross-sectional studies . . . , some degree of fibrosis is found in up to 66% of patients at the time of diagnosis" of NAFLD); Sanjay Agrawal & Herbert L. Bonkovsky, *Management of Nonalcoholic Steatohepatitis*, 35 J. CLIN. GASTROENTEROL. 253, 253 (2002) (Ex. 2) (NASH, "although usually relatively mild, may in some cause fibrosis, cirrhosis, and premature death resulting from liver failure.").

27 Maddrey (10/2/02) Report ¶ 4 (Ex. 326).

28 D. Montgomery Bissell & Jacquelyn J. Maher, *Hepatic Fibrosis and Cirrhosis*, *in* 1 HEPATOLOGY: A TEXTBOOK OF LIVER DISEASE, *supra*, at 395, 395.

29 *See* Kaplowitz Report ¶¶ 16, 36 (Ex. 323).

stage of liver disease in which "groups of hepatocytes become completely encased by fibrous material, and nodules replace normal lobular organization."[30] When liver disease is "moderately advanced," "fibrosis often appears as connective tissue that spans portal and central areas," a condition known as "bridging fibrosis."[31]

3. Mechanisms of Cell Death

Some of the plaintiffs' witnesses base their proposed testimony on theories relating to death of liver cells allegedly attributable to Rezulin.

There are two basic mechanisms of cell death: necrosis and apoptosis.[32] Experts from both sides agree on their basic features.

In necrotic cell death, the cell membrane ruptures, and the contents of the cell are discharged into the surrounding tissue. Among these cellular contents in the liver are enzymes, including alanine aminotransferase ("ALT") and aspartate aminotransferase ("AST") (collectively, "transaminases").[33] Thus, necrotic cell death in the liver in sufficiently large quantities is

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30 Bissell & Maher, *supra*, at 395.

31 *Id*.

32 *See, e.g.*, Caldwell Report ¶ 15 (Ex. 318); Day Decl. ¶ 14 (Ex. 334); *see also* Lefkowitch, *supra*, at 727 ("The term *necrosis* is often used generically to refer to liver cell death, but ideally investigations of cell death distinguish between the pathways of both *necrosis* and *apoptosis*[.]").

33 *See* Lawrence S. Friedman et al., *Laboratory Evaluation of the Patient with Liver Disease*, *in* 1 HEPATOLOGY: A TEXTBOOK OF LIVER DISEASE, *supra*, at 661, 661-62.

accompanied by elevations of liver enzyme concentration in the blood.[34]

In apoptosis, by contrast, the dying cell shrinks and is engulfed and digested by neighboring phagocytes,[35] described in one of the expert reports as "tissue clean up cells."[36] Apoptosis sometimes is known as "programmed cell death" or "cell suicide."[37] Like necrosis, it is "often naturally initiated by the body to eliminate cells that are no longer needed"[38] and is necessary for human survival.[39]

Apoptosis in the liver usually is not accompanied by enzyme elevation because the phagocytes typically devour the apoptotic cells before the latter release their contents into blood. Apoptosis in the liver, however, may result in elevated liver enzymes when it takes place on such a scale that the ability of viable cells to remove dying cells is overwhelmed.[40]

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34 Caldwell Report ¶ 15 (Ex. 318); Reed (8/30/02) Decl. ¶ 11 (Ex. 337).

35 Caldwell Report ¶ 16 (Ex. 318); Day Decl. ¶ 14 (Ex. 334); Bonkovsky Decl. ¶ 12 (Ex. 332).

36 Caldwell Report ¶ 16 (Ex. 318).

37 *See, e.g.*, Day Decl. ¶ 14 (Ex. 334); Bonkovsky Decl. ¶ 12 (Ex. 332); Tr. 5/20/03, at 18 (Smith direct), 154 (Reed direct).

38 Caldwell Report ¶¶ 15, 16 (Ex. 318); *accord* Bonkovsky Decl. ¶ 12 (Ex. 332).

39 *See* Reed (12/9/02) Dep. 18 (Ex. 296); *see also* Pl. Response to Def. Proposed Findings of Fact ¶ 3.6.2 ("Pl. Reply to Def. Facts") (admitting this point).

40 *See* Reed (8/30/02) Decl. ¶ 11 (Ex. 337); Day Decl. ¶ 14 (Ex. 334); Caldwell Report ¶ 16 (Ex. 318); Tr. 5/20/03, at 161 (Reed direct).

B. Drugs, Toxicity to the Liver, and Rezulin

Because the liver "is central to the metabolic disposition of virtually all drugs and foreign substances," liver injury "is a potential complication of nearly every medication that is prescribed."[41] Experts from both sides agree that liver injury caused by drugs is typically categorized as hepatocellular, cholestatic, or mixed based on the pattern of blood test results. Hepatocellular injury is injury to hepatocytes and is manifested by elevated quantities of transaminases in the blood. Cholestatic injury is injury to the liver's ability to produce and excrete bile and is manifested by elevated quantities of alkaline phosphatase and bilirubin. The injury is mixed if features of both hepatocellular and cholestatic injury are present.[42]

In general, drugs are either predictable or unpredictable (idiosyncratic) toxins to the liver, or hepatotoxins. Predictable toxins are dose-dependent. Unpredictable toxins, while capable of producing damage at therapeutic doses, do so rarely.[43]

There is no dispute that a small percentage of patients treated with Rezulin developed reversible elevations of ALT of more than three times the upper limit of normal.[44] The mechanism

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41 William M. Lee, *Drug-Induced Hepatotoxicity*, 333 N. ENG. J. MED. 1118, 1118 (1995) (Ex. 126).

42 Watkins (5/3/01) Decl. ¶ 7 (Ex. 330); Bonkovsky Decl. ¶ 12 (Ex. 332).

43 *See* Davendra Ramkumar & Douglas R. LaBrecque, *Drug-Induced Liver Disease and Environmental Toxins*, *in* 2 HEPATOLOGY: A TEXTBOOK OF LIVER DIEASE, *supra*, at 755, 760.

44 The percentage in the North American clinical trials was 1.9 percent, as compared with 0.6 percent of patients who received a placebo. *E.g.*, Paul B. Watkins & Randall W. Whitcomb, *Hepatic Dysfunction Associated with Troglitazone*, 338 N. ENG. J. MED. 916, 916 (1998) (Ex. 229).

by which Rezulin is toxic to liver cells is not well understood.[45] The defendants' experts believe that Rezulin is an idiosyncratic hepatotoxin, inducing liver injury on an unpredictable basis in a very small number of cases.[46] The plaintiffs' experts believe that Rezulin can be directly toxic to cells, even though the drug exhibits features of idiosyncratic toxicity.[47] Liver injury attributable to Rezulin is predominantly hepatocellular,[48] but the defendants do not dispute, at least for purposes of this motion, that the drug is capable of causing cholestatic or mixed injury.[49]

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45 *See*, *e.g.*, Myung-Ae Bae & Byoung J. Song, *Critical Role of c-Jun N-Terminal Protein Kinase Activation in Troglitazone-Induced Apoptosis of Human HepG2 Hepatoma Cells*, 63 MOLECULAR PHARMACOL. 401, 401-02 (2003) (Ex. 10); William M. Lee, *Drug-Induced Hepatotoxicity*, 349 N. ENG. J. MED. 474, 483 (2003); Vsevolod E. Kostrubsky et al., *The Role of Conjugation in Hepatotoxicity of Troglitazone in Human and Porcine Hepatocyte Cultures*, 28 DRUG METABOLISM AND DISPOSITION 1192, 1192 (2000) (Ex. 119).

46 *See* Maddrey Report ¶ 10 (Ex. 326); Chojkier Report 2 (Ex. 319); *see also* Elizabeth J. Murphy et al., *Troglitazone-Induced Fulminant Hepatic Failure*, 45 DIGESTIVE DISEASES & SCI. 549, 552 (2000) (Ex. 158) ("Whatever the mechanism, hepatotoxicity from troglitazone is clearly idiosyncratic, occurring in a small minority of patients in a dose-independent fashion.").

47 *See* Bonkovsky Decl. ¶ 10 (Ex. 332); Day Decl. ¶ 13 (Ex. 334); Smith (9/02/02) Decl. ¶ 11 (Ex. 339); *see also* P.F. Malet et al., *Direct Hepatotoxicity and Cytoprotection*, *in* D. Montgomery Bissell et al., *Drug-Induced Liver Injury: Mechanisms and Test Systems*, 33 HEPATOL. 1009, 1009 (2001) (Ex. 17) ("Troglitazone-associated hepatotoxicity is a recent example of idiosyncratic, direct hepatocyte toxicity.").

48 Watkins (5/3/01) Decl. ¶ 8 (Ex. 330).

49 *See* footnote 7 above.

C. Patient Population

Type 2 diabetes affects an estimated 16 million Americans.[50] It is associated with obesity, and both obesity and diabetes are associated with NAFLD and NASH.[51] Approximately 50 percent of patients with diabetes have NAFLD.[52] (The prevalence of NAFLD in the general population of the United States was once estimated at 24 percent and is likely higher today.[53]) The percentage of diabetics with NASH is unknown but probably smaller.[54]

D. Evidence of Causation in Medicine

The expert testimony in this case purports to be grounded on a number of scientific and medical studies. For the sake of context, the Court briefly reviews principles regarding the applicability of different kinds of scientific and medical research.

The "gold standard" for determining the relationship between a drug and a health outcome is the clinical trial. In such investigations, subjects are assigned randomly to one of two groups: one exposed, and the other not exposed, to the drug of interest. Such studies, however, are

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50 *See* Paul Angulo, *Nonalcoholic Fatty Liver Disease*, 346 N. ENG. J. MED. 1221, 1222 (2002) (Ex. 5); CENTERS FOR DISEASE CONTROL AND PREVENTION, DIABETES: A SERIOUS PUBLIC HEALTH PROBLEM 2 (2000) (Ex. 349).

51 Angulo, *supra*, at 1221.

52 *Id*. at 1222.

53 *See* Sanjay Agrawal & Herbert L. Bonkovsky, *Management of Nonalcoholic Steatohepatitis*, 35 J. CLINICAL GASTROENTEROL. 253, 253 (2002) (Ex. 2).

54 *See* Caldwell (11/19/02) Dep. 136 (Ex. 263).

not always available, at least in part because ethical constraints preclude exposing human beings to agents known or thought to be toxic.[55] Thus, other kinds of evidence often are used to assess whether a drug or agent is related to the risk of developing a certain condition.

Chief among these are observational epidemiological studies, in which subjects that were exposed to an agent prior to the investigation are compared with subjects not so exposed.[56]

Another type of information used by physicians and medical researchers is the case report, which is a description of a particular patient's clinical history and symptoms. As explained in the *Reference Manual on Scientific Evidence*:

> "Case reports lack controls and thus do not provide as much information as controlled epidemiological studies do. However, case reports are often all that is available on a particular subject . . . . Casual attribution based on case studies must be regarded with caution. However, such studies may be carefully considered in light of other information available, including toxicological data."[57]

The difficulty with case reports, in other words, is distinguishing between association and causation. Simply because a patient exposed to a particular substance exhibited a set of symptoms does not mean that it was the substance that caused the symptoms.

In addition to research on humans, scientists often perform experiments on living animals, such as rats, mice, and monkeys. The advantages of such studies include the fact that they can be conducted as true experiments, with exposure controlled and measured and ethical limitations

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55 Michael D. Green et al., *Reference Guide on Epidemiology*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 338-39 (Fed. Jud. Ctr., 2d ed. 2000) (hereinafter *Reference Guide on Epidemiology*).

56 *Id*. at 339-45.

57 *Reference Guide on Medical Testimony*, *supra*, at 475.

diminished.[58] Nevertheless, although it is "a basic principle of toxicology and pharmacology" that "a compound causing an effect in one mammalian species [usually] will cause it in another,"[59] extrapolation from animal studies to humans cannot be done uncritically. For one thing, different species have important physiological differences. For another, the high doses often used in animal studies may not correspond to considerably lower concentrations of a drug or other substance to which humans are in reality exposed.[60]

Finally, researchers frequently conduct experiments on cell and tissue cultures. These experiments, sometimes referred to as *in vitro* studies to distinguish them from studies performed *in vivo*, meaning on live humans and animals, also are subject to the problem of extrapolation. It is not always clear that "one can generalize findings from the artificial setting of tissues in laboratories to whole human beings."[61]

IV. The Proposed Testimony

The defendants do not challenge the admissibility of expert testimony to the effect that Rezulin is capable of causing liver injury that results in elevation of liver enzymes. They train their fire only on opinion testimony that the drug is capable of doing so "silently," that is, without

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58 *Reference Guide on Epidemiology*, *supra*, at 345-46.

59 Bernard D. Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 401, 410 (Fed. Jud. Ctr., 2d ed. 2000) (hereinafter *Reference Guide on Toxicology*).

60 *Reference Guide on Epidemiology*, *supra*, at 346.

61 *Id*. at 346; *see also Reference Guide on Toxicology*, *supra*, at 410.

markedly elevating those enzymes approximately concurrently with treatment.[62] The defendants challenge aspects of the opinions of five expert witnesses.

Before reviewing the challenged testimony, a preliminary note is in order. The plaintiffs' counsel at every stage have gone further than their experts. They have formed hypotheses that the experts nowhere mentioned, they have forged connections that the experts stopped short of drawing, and they have portrayed as sturdy hypotheses that the experts espoused hesitantly if at all. None of these elaborations by counsel is relevant. The subject of this motion is the proposed testimony of experts, not the theories of the lawyers.

A. The Experts and Their Opinions

1. Dr. Smith

The opinion of Dr. Martyn T. Smith, who testified at the evidentiary hearing, is central to this motion. Dr. Smith is a toxicologist. He holds a Ph.D. and is a professor in the Division of Environmental Health Sciences at the University of California at Berkeley's School of Public Health. He is not a clinician and has no training in hepatology.[63]

Dr. Smith opines that "[a] careful review of all of the literature allows one to conclude to a reasonable degree of scientific probability that [Rezulin] more likely than not . . . can damage

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62 The plaintiffs argue that the term "silent injury" is a "misnomer" because this type of liver injury will be manifested by observable symptoms besides elevated enzymes. Pl. Reply to Def. Facts ¶¶ 1.1(a), 3.11, 3.12. But it was the plaintiffs' expert, Dr. Smith, who used the term in this way. *See* Smith (9/2/02) Decl. ¶ 32 (Ex. 339); Smith (3/17/03) Decl. ¶ 9 (Ex. 340). The Court is not impressed with the plaintiffs' attempt to disown the terminology used by the very expert whose testimony is the primary subject of this motion. In this opinion, "silent injury" will be used as a convenient shorthand for injury that occurs in the absence of an elevation of one of the four substances.

63 Smith (9/2/02) Decl. ¶¶ 1-2 (Ex. 339); Tr. 5/20/03, at 95.

the liver 'silently' because apoptosis does not cause elevation of liver enzymes in serum."[64] He states "that to a reasonable degree of scientific probability troglitazone[65] can induce apoptotic death of cells in the liver in humans *in vivo*."[66]

Dr. Smith offers two major mechanisms by which Rezulin could cause apoptosis. The first involves a cascade of chemical events in which the mitochondria cease functioning normally and release a protein into the cytoplasm that triggers apoptosis.[67] The second involves the bile salt export pump, or BSEP. The BSEP is a protein in the plasma membranes of hepatocytes that pumps bile salt out of the cell. Dr. Smith states that Rezulin can interfere with the functioning of the pump, leading to the build-up of toxic bile salts in the cells and that this condition triggers apoptosis.[68]

2. Dr. Reed

Dr. John C. Reed's opinion also is a major subject of this motion. Dr. Reed is the president and chief executive officer of the Burnham Institute, a research center in La Jolla,

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64 Smith (9/2/02) Decl. ¶ 32 (Ex. 339).

65 Troglitazone is the chemical name for Rezulin. It sometimes is referred to as well by the abbreviations TRO and TGZ. The Court uses these designations interchangeably.

66 *Id*. ¶¶ 26; *accord id.* ¶¶ 21-22.

67 *Id*. ¶¶ 27, 32(c).

68 *Id*. ¶¶ 28-29, 32(c).

California.[69] He holds an M.D. and a Ph.D.[70] and has described himself as follows: "I don't consider myself a liver expert or hepatology expert. I consider myself an apoptosis expert."[71] Dr. Reed testified at the evidentiary hearing.

Dr. Reed's declarations are intended to "address[] the evidence that Rezulin (troglitazone) induces apoptosis in human and animal cells."[72] Dr. Reed's declarations do not say that a Rezulin-induced injury could be silent.[73] His testimony therefore is relevant only to the extent that it provides support for the other experts – principally Dr. Smith – who are willing to draw that conclusion.

3. Dr. Julie

Neil Julie, M.D., practices gastroenterology and hepatology in a Maryland suburb of Washington, D.C.,[74] and also testified at the evidentiary hearing. His initial declaration is organized for the most part as a set of conclusions, each in the form of a single sentence and each followed by the statement that "[m]y opinions are based upon my education, training and experience as well as

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69 Reed (8/30/02) Decl. ¶ 1 (Ex. 337); Tr. 5/20/03, at 153.

70 Reed (8/30/02) Decl. ¶ 1 (Ex. 337).

71 Reed (12/9/02) Dep. 129 (Ex. 296).

72 Reed (8/30/02) Decl. ¶ 8 (Ex. 337).

73 Dr. Reed did testify in his deposition that it was his "opinion that Rezulin can cause injury silently without increase in ALT unless the injury is in its advanced stages or during fulminant tissue injury[.]" Reed (12/9/02) Dep. 64 (Ex. 296).

74 Julie (9/3/02) Decl. ¶ 1 (Ex. 335).

my review of the following materials" and then a long list of documents, medical articles, and testimony. The conclusions relevant here are that "Rezulin causes a multitude of hepatocellular injuries including but not limited to . . . apoptosis . . . ." and "Rezulin liver injury can occur without an elevation of AST and ALT."[75]

The plaintiffs submitted a second declaration from Dr. Julie to address:

> "the tools a medical doctor should appropriately utilize in order to diagnose a medical condition generally and, more specifically, the use of differential diagnosis[76] with respect to a Rezulin-related hepatic injury, including evidence of studies showing mitochondrial damage and apoptosis caused by Rezulin."[77]

Dr. Julie concludes: "it is my opinion that it would be inappropriate to broadly conclude that a patient did not suffer a drug-induced liver injury from Rezulin simply based upon the absence of a marked elevation in liver enzymes."[78] In support of this statement, Dr. Julie states among other things that "[a] physician performing a differential diagnosis must consider . . . relevant scientific evidence" of Rezulin's "toxic effect on mitochondria and its ability to induce cell death via apoptosis."[79]

Dr. Julie acknowledged that his view that Rezulin is toxic to the mitochondria is

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75 *Id*. at 13-14, 17-18.

76 Differential diagnosis is discussed in section VII below.

77 Julie (3/18/03) Decl. ¶ 2 (Ex. 336).

78 *Id*. ¶ 23.

79 *Id*. ¶ 18.

derived from the opinions of Drs. Smith and Reed and the articles they cite for support.[80]

4. Dr. Day

Dr. Christopher P. Day is a research scientist and practicing hepatologist. He holds an M.D. and a Ph.D. and is a professor at the University of Newcastle upon Tyne in the United Kingdom.[81] His report is concerned mainly with illustrating the varied ways in which Rezulin and other drugs can injure the liver.

As relevant here, Dr. Day would testify that "a biologically plausible explanation for why many patients with liver disease post-exposure to troglitazone may not have had significant elevations of their transaminase levels" is that cells undergoing apoptosis are consumed by surrounding cells.[82] Dr. Day's declaration further states that cholestasis and mitochondrial injury are "biologically plausible mechanisms for the development of apoptosis in patients exposed to troglitazone."[83]

The Court notes that cholestatic injury normally results in increased bilirubin or

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80 Tr. 5/21/03, at 258-60.

81 Day Decl. ¶¶ 1-9 (Ex. 334).

82 *Id.* ¶ 14; *accord* ¶ 19 ("I find the association of troglitazone with apoptosis to be not only 'compelling' but also, more likely than not, the cause of cases of hepatotoxicity secondary to troglitazone which have manifested without significant elevation of liver transaminase levels.").

83 *Id.* ¶ 28.

alkaline phosphatase[84] and that Dr. Day does not say that apoptosis related to cholestasis, if it occurs at all, would not affect bilirubin and alkaline phosphatase levels. Furthermore, Dr. Day does not say that apoptosis related to mitochondrial injury could cause injury without an elevation of transaminases. In other words, Dr. Day does not appear to offer the testimony that the defendants are seeking to exclude, which is the opinion that Rezulin can cause liver injury without an elevation in at least one of the four substances. His testimony therefore is of limited relevance. The Court nonetheless considers it insofar as it could be read to suggest that any injury caused by Rezulin would be silent.

5. Dr. Bonkovsky

Herbert L. Bonkovsky, M.D., is a hepatologist and a professor at the University of Connecticut Medical School.[85] The thrust of his opinion is that Rezulin "causes a wide spectrum of liver disease."[86] He states among other things that liver inflammation "such as that caused by Rezulin" can lead to bridging fibrosis and cirrhosis and that "[t]hese injuries have been observed in many cases with either normal or near normal values of ALT."[87] Dr. Bonkovsky, however, does not say that any such injuries that have been observed were due to Rezulin, nor does he provide any support for the statement that those injuries occurred with normal values of ALT.

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84 *See* section III.B above; *see also* Day Decl. ¶ 33 (Ex. 334) ("the most serious hepatic 'signal' to be carefully considered in a clinical trial setting is jaundice (defined as a serum bilirubin exceeding [a particular concentration]).").

85 Bonkovsky Decl. ¶¶ 1-5 (Ex. 332).

86 *See id*. ¶ 25.

87 *Id*. ¶ 29.

Elsewhere in his declaration Dr. Bonkovsky opines that apoptosis[88] and inhibition of the BSEP[89] are plausible mechanisms of injury due to Rezulin. In addition, Dr. Bonkovsky's opinion reviews some of the research cited in the reports of Drs. Reed and Smith for the proposition that Rezulin can affect the mitochondria.[90] But Dr. Bonkovsky does not attempt to relate these statements, nor does he state that an effect on the mitochondria could cause apoptosis or that any injuries due to inhibition of the BSEP or apoptosis would be silent. He states without significant elaboration that he agrees with the views expressed in Dr. Smith's report "on the various mechanisms of action associated with Rezulin,"[91] but there is no indication that Dr. Bonkovsky intends to testify that Rezulin can cause liver injury silently.

6. Summary

To the extent the experts would testify that Rezulin can cause "silent" liver injury, they have postulated a causal chain in which Rezulin can affect the mitochondria or the BSEP and thus trigger apoptosis, which would be injurious but silent. A graphical representation of the theory might be useful:

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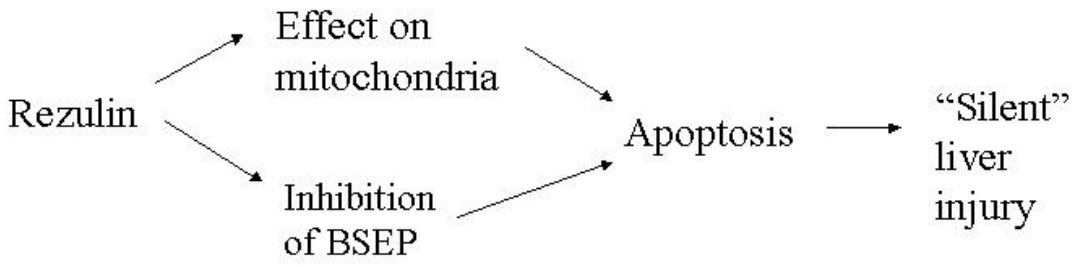
88 *Id.* ¶ 17.

89 *Id.* ¶ 18.

90 *See id.* ¶¶ 16-17.

91 *Id.* ¶ 19.



B. The Science upon Which the Experts Rely

The Court now will review the scientific research that the experts cite in support of their opinions. As will be discussed in a later section, the Court does not necessarily agree that all of the cited studies support the conclusions. The Court's concern for the time being, however, is to present the experts' own case. Nonetheless, at certain points in the following discussion, the Court will add its own observations – for example, comments on aspects of the studies, on the nature of the connections between the studies and the expert opinions, or on the absence of certain kinds of evidence – when it believes that additional information is essential to evaluate the testimony in question.

As an initial matter, the plaintiffs' experts cite no studies that say that Rezulin can cause a silent liver injury. There are no clinical trials and no observational epidemiological studies supporting the plaintiffs' position. Nor have the plaintiffs pointed to any clinical case in which Rezulin was believed to have caused such an injury.[92] Rather, the opinions at issue on this motion

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[92] The case reports that the plaintiffs and their experts say are examples or illustrations of an injury silently caused or exacerbated by Rezulin do not support their assertions.

Dr. Smith at the hearing pointed to data on one patient with NASH in the Caldwell et al. (2001a) study (the conventions used in this opinion to refer to scientific studies are explained in the following footnote) who had advanced bridging fibrosis that progressed during six months of Rezulin treatment to frank cirrhosis without an elevation in liver

are based on studies that the experts say support individual links in their causal chain. In particular, the experts have cited studies that connect Rezulin to apoptosis, studies that connect Rezulin to mitochondrial damage, and studies that connect Rezulin to an effect on the BSEP. Nearly all of these studies were conducted *in vitro*.

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enzymes. He acknowledged that "this is the only example I know of in the peer-reviewed literature that exacerbation of a pre-existing liver condition occurs in a silent manner." Tr. 5/20/01, at 94. The implication – one not drawn by the study's authors – is that Rezulin in this case caused a silent injury, namely the progression from fibrosis to cirrhosis. *See id.* at 94-95. But this is entirely unsubstantiated and a classic example of the *post hoc ergo propter hoc* (i.e. after the fact, therefore because of the fact) fallacy.

As discussed in section III.A.2 above, it is not at all rare for a patient to undergo a progression from advanced bridging fibrosis to cirrhosis in the absence of Rezulin. Thus, the question is whether *this* patient's progression can be attributed to Rezulin. Dr. Smith pointed to no evidence to support his belief that this timeline was unusually short for this progression, and he admitted that he has no expertise on progression from fibrosis to cirrhosis. *See id.* at 95-96. Dr. Julie, who does have clinical expertise, said that he would expect this progression normally to take at least two to five years, but that "[w]ithout knowing the general clinical history of the patient, however, I can't really apply that." Tr. 5/21/03, at 262. Dr. Julie acknowledged that a biopsy will fail to detect cirrhosis in a certain percentage of cases. *Id*. at 273-75. Because Dr. Julie was unwilling to draw the very conclusion required to support the statement that Dr. Smith essentially admitted he was not qualified to make, there is no reliable basis for concluding that the patient in the Caldwell et al. (2001a) study is an example of liver disease or injury silently caused or exacerbated by Rezulin.

Similarly, Dr. Julie's second declaration cites four case reports in which Dr. Julie says autopsies and biopsies revealed "acidophilic bodies," which are considered evidence of apoptosis, *see* PETER J. SCHEUER & JAY H. LEFKOWITCH, LIVER BIOPSY INTERPRETATION 365 (6th ed. 2000) (Ex. 189)). *See* Julie (3/18/03) Decl. 14-15 (Ex. 336). One of those cases specifically states that "[a]cidophilic or apoptotic change of the liver cells or Mallory bodies was rarely found." Fukano et al. (2000), at 251. The other three patients did exhibit acidophilic bodies, but they experienced elevated enzyme levels as well. *See* Herrine & Choudhary (1999); Murphy et al. (2000) (case 3); Kohlroser et al. (2000) (patient 1). These cases therefore do not speak to the issue of silent apoptotic injury.

1. Early Links in the Proposed Causal Chain: The Claim that Rezulin Causes Apoptosis Through Effects on the Mitochondria or the BSEP

a. Studies Connecting Rezulin to Apoptosis

The Court begins with studies cited by the experts for the proposition that Rezulin caused apoptosis in certain kinds of cells.

At the outset, it is important to note that none of these studies dealt with normal human liver cells. The plaintiffs and their experts imply that Kostrubsky et al. (2000),[93] a study that found that Rezulin was toxic to normal human liver cells at certain concentrations, shows that Rezulin produces apoptosis. That study, however, says nothing at all about whether the cell death occurred via apoptosis or necrosis.[94] The same is true of several other studies cited by the plaintiffs and their experts, including Ramachandran et al. (1999).[95]

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93 The Court refers to the studies by the name of the lead author (or both authors, if there are two) together with the year of publication. Where this opinion cites more than one study published by an author in the same year, a letter is attached to the year. The Appendix lists each study's full citation.

94 The plaintiffs' brief, and Dr. Julie's declaration in identical language, describe this study as showing that "[t]roglitazone induces apoptosis in human liver and/or smooth muscle cells." Pl. Mem. 31 n.72; Julie (3/18/03) Decl. 12 (Ex. 336). This is a mischaracterization.

95 The plaintiffs nevertheless contend that "apoptosis was the likely mechanism of cell death in the studies by Kostrubsky and Ramachandran," Pl. Reply to Def. Facts ¶ 7.2(a). This inference is unreliable. Dr. Smith initially testified that the measurement technique used by Ramachandran et al. (1999) implied that the cell remnants more likely than not were the products of apoptosis rather than necrosis, Tr. 5/20/01, at 62, but then repudiated this same testimony under questioning by the Court:

> "Well, your Honor, I am not trying to mislead you into thinking that these six studies in human hepatocytes [including Kostrubksy et al. (2000) and Ramachandran et al. (1999)] measure apoptosis. All that they do is show that the troglitazone has the potential to be cytotoxic to these cells either by apoptosis or necrosis . . . . I'm not trying to mislead you in the fact that these particular studies show that troglitazone can produce apoptosis in human hepatocyte cultures, just

The experts cite one study in which Rezulin was found to cause apoptosis in rat hepatocytes. Toyoda et al. (2001) found that Rezulin produced this effect at concentrations of 15 μM[96] and above.[97] Furthermore, a Warner-Lambert scientist tentatively reached the same conclusion from the company's own data.[98]

The experts cite four[99] studies in which Rezulin was found to produce apoptosis in human liver cancer cells. Bae and Song (2003), Toyoda et al. (2002), Yoshizawa et al. (2002), and Yamamoto et al. (2001) observed that Rezulin produced this result in a dose-dependent fashion above certain concentrations.

In addition, the experts cite a number of studies in which Rezulin at certain concentrations produced apoptosis in cultured cancer cells of other organs. Harris and Phipps (2002) found that troglitazone induces apoptosis in malignant white blood cells. Ohta et al. (2001) observed

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that they would cause cellular death." *Id*. at 66-67.

96 "μM" is a symbol for "micromolar," a measure of the concentration of a solution. A one-molar solution contains one mole of solute per liter. A one micromolar solution contains one one-millionth of a mole of solute per liter. A mole of any substance is 6.024×10^{23} molecules of that substance; a micromole is 6.024×10^{17} molecules. Thus a 15 μM solution of troglitazone contains 9.036×10^{18} troglitazone molecules per liter of solution. *See* HARRY H. SISLER ET AL., GENERAL CHEMISTRY: A SYSTEMATIC APPROACH 85-86, 277-78 (2d ed. 1959).

97 Toyoda et al. (2001) also tested the effect of adding albumin, a blood serum protein. These aspects of the study are discussed in section VI.D.3.b.

98 *See* Memorandum from Kan He to Thomas Woolf et al. 4 (March 11, 1999) (Ex. 367).

99 Dr. Julie cites a fifth, Koga et al. (2001), but that study, which was published before the other four, did not observe apoptosis and specifically stated that "it remains to be elucidated whether or not [mitochondrial damage attributable to troglitazone] causes slow apoptosis in hepatoma [i.e. liver cancer] cells." Koga et al. (2001), at 1096.

a similar result in thyroid cancer cells. Tsubouchi et al. (2000) found the same in lung cancer cells. Guan et al. (1999) did so in bladder cancer cells, and Takahashi et al. (1999) and Sato et al. (2000) obtained this result in stomach cancer cells. Finally, Dr. Reed cites a trio of cases on prostate cancer cells, but they did not find that Rezulin produces apoptosis in human cells.[100]

Several of the studies on cancer cells examined the effect of Rezulin in concert with other substances. For example, the Kim et al. (2002) study examined the effect on lines of ovarian cancer cells of combining an anti-tumor agent known as TRAIL with troglitazone. The researchers found that troglitazone combined with TRAIL (but neither alone) killed tumor cells; the mechanism was believed to be apoptosis. Similarly, Elstner et al. (1998) found that the combination of troglitazone and another chemical (but neither by itself) caused apoptosis in human breast cancer cells.

Finally, the experts cite studies on what Dr. Reed describes as "normal" cells from other organs.[101] Gouni-Berthold et al. (2001) and Okura et al. (2000) obtained results suggesting that

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Dr. Reed's first declaration says: "The types of cancer cells which TGZ has been reported to kill (through the apoptosis mechanism) include cancers of the . . . prostate (Kubota, et al. 1998; Butler, et al 2000; Mueller, et al 2000) . . . ." Reed (8/30/02) Decl. ¶ 13 (Ex. 337). His second declaration implies that Kubota et al. (1998) found that Rezulin caused apoptosis in "human prostate cancer cells." Reed (2/25/03) Decl. 4 (Ex. 338).

These citations are incorrect or misleading. Kubota et al. (1998) found only that Rezulin caused apoptosis in prostate cancer tissue taken from mice. He did not report apoptosis in human prostate cancer tissue. *See* Kubota et al. (1998), at 3348. Similarly, Mueller et al. (2000) looked for apoptosis but did not find it. *See* Mueller et al. (2000), at 10992. And Butler et al. (2000) simply does not concern Rezulin at all.

The Court is troubled by the fact that a self-described apoptosis expert's report includes so many inaccuracies.

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Reed (8/30/02) Decl. ¶ 13 (Ex. 337).

troglitazone caused apoptosis in cultures of a type of blood vessel cell taken from rats and associated with atherosclerosis in humans. Yamazaki et al. (2002) and Kawahito et al. (2000) derived a similar result for cultures of a type of cell that destroys the joints of patients with rheumatoid arthritis because it proliferates like a tumor. And Rovin et al. (2002) found that troglitazone induces cell death believed to be apoptotic in a type of kidney cell that proliferates in response to injury but that can cause kidney failure if the proliferation is excessive.

b. Studies Connecting Rezulin to Mitochondrial Damage

In addition to the studies that show apoptosis from Rezulin, albeit not in normal human liver cells, the experts cite studies showing that Rezulin can affect the mitochondria of liver cells. A preliminary clarification is called for. Toxicity from Rezulin linked to mitochondrial damage is not necessarily relevant to the silent injury theory. It is uncontested that an injury would not be silent if it occurred by necrosis. The studies on mitochondria are relevant to the silent injury theory set forth in the expert reports only to the extent that those studies can be used to connect Rezulin with apoptosis.

The experts cite a number of studies in which Rezulin caused morphologic, or structural, changes to mitochondria. Caldwell et al. (2001a) administered normal doses of Rezulin to NASH patients for six months and examined, among other things, their mitochondria. These investigators found that more of the mitochondria had a misshapen and unusually elongated appearance after treatment. They found as well "a decrease in the mean total number of mitochondria . . . and an increase in the mean percentage of mitochondria that were enlarged and contained

intramitochondrial crystals . . . but neither change was statistically significant."[102]

Although Drs. Smith's and Reed's expert reports do not mention it, these researchers looked for evidence of apoptosis. They examined the post-treatment biopsies of five patients with an electron microscope and found that "features of apoptosis (bleb formation, nuclear fragmentation) were not evident."[103] They then applied a biochemical marker that detects apoptosis and found "[n]o statistically significant difference between the before and after specimens[.]"[104]

Apart from Caldwell et al. (2001a), the other mitochondria studies all were performed *in vitro*. Shishido et al. (2003) applied troglitazone at concentrations up to 50 μM – the researchers chose that concentration because it had prevented the cells from proliferating without inducing apoptosis in a previous study performed on liver cancer cells[105] – to an immortalized[106] cell line and found "marked enlargement"[107] and other abnormalities in the mitochondria. Tirmenstein et al. (2002) applied the drug to liver cancer cells and found "extensive alterations in mitochondrial

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102 Caldwell (2001a), at 521-22.

103 *Id*. at 522.

104 *Id*. at 522-23.

105 Shishido et al. (2003), at 137. The previous study was Koga et al. (2001).

106 Researchers often use cells that have been genetically engineered to reproduce indefinitely (i.e., immortalized); cultures of many types of normal cells, including liver cells, die after a certain period of time. *See* Tr. 5/21/03, at 74, 76 (Smith direct), 204-05 (Reed cross).

107 Shishido et al. (2003), at 140.

morphology."[108]

Several of the studies cited by the experts measured a quantity known as the mitochondrial membrane potential, which is the electrical gradient, or polarization, between the outside and inside of a mitochondrion. A decrease in this polarization indicates that the mitochondria are not functioning normally. Haskins et al. (2001) found that troglitazone at certain concentrations produced a decrease in the mitochondrial membrane potential in rat hepatocytes and in the hepatocytes of one diabetic human donor, but not in the cells of another diabetic donor. These researchers wrote that "[f]uture studies should address the downstream effects of these changes, since nuclear condensation and apoptosis are observed as late effects that are shared by" troglitazone's chemical family.[109] Shishido et al. (2003) and Tirmenstein et al. (2002) found that troglitazone at certain concentrations depolarized the mitochondrial membrane in the immortalized liver cells and in liver cancer cells, respectively.

Dr. Smith's reports, but not Dr. Reed's, argue that the above-described effects on the mitochondria link Rezulin to apoptosis. Dr. Smith begins with the statement that the "[t]he decline in mitochondrial transmembrane potential seen in these experiments is called the mitochondrial permeability transition."[110] Dr. Smith continues:

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108 Tirmenstein et al. (2002), at 134.

109 Haskins et al. (2001), at 436.

110 Smith (3/17/03) Decl. ¶ 7 (Ex. 340).

Dr. Smith's terminology is questionable. The change in mitochondrial membrane potential is not "called the mitochondrial permeability transition." The mitochondrial membrane potential is, as just explained, the electrical differential across the membrane. The mitochondrial permeability transition is a change in the chemical permeability of the

> "During the mitochondrial permeability transition, pores in the mitochondrial membrane are opened and [a protein known as] cytochrome c is released into the cytoplasm. . . . The cell 'knows' the cytochrome c should be normally be [*sic*] inside the mitochondria, so when it leaks out it acts as a signal telling the cell that the mitochondria are badly damaged, and this stimulates the cell to commit suicide (i.e. apoptosis)[.]"[111]

Dr. Smith here cites Ravagnan et al. (2002). That article[112] states that once a cell has been induced to die, "the outer mitochondrial membrane becomes completely permeabilized to proteins, resulting in the leakage of potentially toxic mitochondrial intermembrane proteins" – the authors include cytochrome c in this category – "that orchestrate the degradation phase of apoptosis."[113] Ravagnan et al. (2002) thus does not say, as Dr. Smith seems to, that mitochondrial change (due to Rezulin or otherwise) alone can be an *independent cause* of apoptosis. Rather, the authors view certain mitochondrial changes as themselves products of some prior cause of cell death and as one *step* in a chain of events that leads to apoptosis. Another article cited by Dr. Smith, Bissell et al. (2001), reflects a similar understanding.[114]

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mitochondrial membrane. The phenomena may be related, but the concepts are different. Indeed, Tirmenstein et al. (2003), one of the two articles that Dr. Smith himself cites to support this discussion, specifically states that "[i]t is important to emphasize that mitochondrial depolarization and mitochondrial permeability transition are distinct events. . . . Mitochondrial membrane depolarization is known to promote opening of the permeability transition pore[.]" Tirmenstein et al. (2003), at 283.

111 Smith (3/17/03) Decl. ¶ 8 (Ex. 340).

112 Ravagnan et al. (2002) is a review article. A review article critically examines a body of research but does not report any original results of its own. *See, e.g.*, Tr. 5/20/03, at 20 (Smith direct).

113 Ravagnan et al. (2002), at 132.

114 *See* J. H. Hoofnagle et al., *Drug-Induced Mitochondrial Injury*, *in* Bissell et al. (2001), at 1011, 1012: "Mitochondria also play a major role in apoptotic pathways, through induction

A cited study that does agree with Dr. Smith[115] is Kim et al. (2003). These researchers found that the change in permeability of the mitochondrial membrane triggered cell death in rat hepatocytes. This paper, however, reports that the cell will undergo apoptosis – as opposed to necrosis – only if there is sufficient ATP. The organized death of the cell is a process that consumes energy, and without energy (in the form of ATP), the cell defaults to the necrotic mode of death.[116]

Another paper that agrees that the depolarization of the mitochondrial membrane itself can be a cause of cell death is Tirmenstein et al. (2002). This study, however, does not indicate whether the cell death occurs via apoptosis or necrosis, and it specifies that troglitazone leads to a decrease in the amount of ATP in the cell. Furthermore, the concentrations at which troglitazone produced cell death in this study were higher than those at which it began to affect the mitochondria.

Dr. Smith continues:

> "A protein in the cytoplasm, called Bax, then migrates to the mitochondrial membranes and accelerates the apoptotic process by making the mitochondrial membrane even more permeable, thus further releasing even more cytochrome c into the cytoplasm thereby speeding up the apoptotic process[.]"[117]

Here Dr. Smith cites Smaili et al. (2001). Those researchers found that a decline in the mitochondrial

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of the mitochondrial permeability transition pore, which results in a rapid increase in mitochondrial membrane permeability and release of cytochrome c and other proapoptotic factors."

115 The citation to this study appeared in an earlier section of Dr. Smith's second report. The section was extremely similar to, and appears to be a variant draft of, certain sections in the second reports of Drs. Reed and Julie. *See* Smith (3/17/03) Decl. 4-6 (Ex. 340); Reed (2/25/03) Decl. 6-8 (Ex. 338); Julie (3/18/03) Decl. 13-14 (Ex. 336).

116 Lemasters (1999) and Lemasters et al. (1998) are in accord.

117 Smith (3/17/03) Decl. ¶ 8 (Ex. 340).

membrane potential precedes the attachment of Bax to the mitochondria in cells genetically engineered to overproduce Bax. The authors sum up the implications of their research this way: "our results suggest that alterations in mitochondrial energization *associated with* apoptosis can initiate Bax docking to mitochondria."[118] The study, in other words, says nothing about whether mitochondrial dysfunction (whether caused by Rezulin or otherwise) is an independent cause of apoptosis. This study, like the research reviewed in Ravagnan et al. (2002), created conditions known to induce apoptosis and then examined the sequence of events within the cell.

Dr. Smith concludes:

> "For TRO induced liver cell apoptosis, this process has recently been studied in detail by Bae and Song . . . . They found a critical role for Bax and [a protein known as JNK] activation in TRO induced liver cell apoptosis. . . . TRO . . . induced apoptosis that was preceded by activation of JNK . . . and increased levels of Bax [and] release of cytochrome c . . . ."[119]

Bae and Song (2003), as mentioned above, found that troglitazone causes apoptosis in liver cancer cells. They found as well that TRO increases the levels of proteins associated with apoptosis, including Bax and cytochrome c. They did not, however, examine the mitochondria.

c. Studies Connecting Rezulin to an Effect on the BSEP

Dr. Smith's other proposed mechanism through which Rezulin allegedly could cause silent injury involves the BSEP. As with the evidence on mitochondria, and for the same reasons, any effect on the BSEP is relevant to the silent injury theory only to the extent that it connects

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118 Smaili et al. (2001), at 909 (emphasis added).

119 Smith (3/17/03) Decl. ¶ 8 (Ex. 340).

Rezulin with apoptosis.

The experts cite several articles in which Rezulin was found to interfere with the ability of cells to export bile salts. Preininger et al. (1999) reported that troglitazone interfered with the flow of bile in isolated rat livers. Two studies by Funk et al. confirmed this result in live rats; they found that when troglitazone was administered to rats, there was an increase in the concentration of bile acid in the rats' blood plasma believed to have been caused by interference with the BSEP. Elevation of bile acid is analogous to elevation of bilirubin;[120] both indicate a cholestatic injury.

To connect the presumed effect on the BSEP to apoptosis, Dr. Smith and Dr. Reed cite a group of studies and review articles.[121] All are concerned with elucidating the biochemical mechanisms by which the build-up of bile in the liver can produce apoptosis.

2. The Last Link in the Chain: The Claim that Apoptosis from Rezulin Causes Silent Injury

The plaintiffs' experts have cited no evidence that any apoptosis caused by Rezulin can result in a silent injury. That is, the plaintiffs' experts have offered no evidence that apoptosis caused by Rezulin, if any, occurs at a clinically significant level or, even if it does, that the resulting injury would remain silent.

The following exchange occurred during Dr. Smith's testimony:

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120 *See* Lawrence S. Friedman et al., *Laboratory Evaluation of the Patient with Liver Disease*, *in* 1 HEPATOLOGY: A TEXTBOOK OF LIVER DISEASE, *supra*, at 661, 671.

121 The most relevant appear to be Jaeschke et al. (2002), Sodeman et al. (2000), Miyoshi et al. (1999), Faubion et al. (1999), Patel et al. (1999), and Kwo et al. (1995).

"The Court: I think . . . it is your view . . . that doses of Rezulin that have been shown to be cytotoxic in cell studies obviously can be achieved in some human cells. We agree so far?

"The Witness: Sure. I agree on it.

"The Court: . . . [W]hat, if anything, does that tell us on an empirical basis, as opposed to a theological basis, [about] whether achievement of those doses in some undefinable proportion of liver cells has any serious adverse consequences for anybody? . . . Isn't it entirely possible, and indeed probable, that there is some minimal number or proportion of liver cells that have to be killed off before there is any interference with the liver's functioning that matters to anybody?

"The Witness: That is true.

"The Court: Right. Do we know what this, and how it relates to the effect of Rezulin?

"The Witness: I don't think we do know, your Honor."[122]

Dr. Reed testified in a similar way. The following exchange occurred during his cross-examination:

"Q. Doctor, you testified that you believe it is possible that Rezulin could be inducing a low level of apoptosis in human livers, is that correct?

"A. Yes, I believe that is possible.

. . .

"Q. . . . [D]o you have any study or any data to support that sustained apoptosis has resulted in clinical injury in a patient taking Rezulin?

"A. Such a study has not been performed, to my knowledge."[123]

Dr. Reed further testified as follows:

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[122] Tr. 5/20/03, at 143-44.

[123] Tr. 5/21/03, at 214.

"The Court: So just to try to put it in bottom line colloquial terms, even assuming . . . everything you and Dr. Smith have said about the capability of Rezulin to induce apoptosis in particular liver cells at what I will call for the sake of quickness relevant concentrations, we have no empirical data that indicates to us how many or what percentage of the liver cells are injured in that way in vivo and what the threshold level of injury, in terms of numbers or proportion of liver cells, needs to be before there is any clinical injury to the patient?

"The Witness: No, we really don't know the percentage. All we know is, as I have said, one out of every 50 people has sufficient cell death occurring . . . that their transaminase levels rose when they took the drug."[124]

C. Arguments that Rezulin Can Cause Silent Liver Injury Through Mechanisms Other than Apoptosis

In addition to the apoptosis theory, the plaintiffs' counsel have argued that liver injury caused by Rezulin can be silent either because Rezulin suppresses the production of enzymes in the liver or because the enzymes might have been depleted already in a patient with pre-existing liver injury.[125] The logical implication is that even if the apoptosis theory discussed above were unsubstantiated or incorrect, plausible mechanisms by which Rezulin can cause silent liver injury would remain. The problem is that these mechanisms, for the most part, were proposed by the plaintiffs' counsel, not their experts. To the limited extent that they have been adopted by the experts, they are not supported.[126] The only physiological explanation offered by the plaintiffs'

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124 *Id.* at 230-31.

125 Pl. Mem. 14, 17.

126 For the proposition that Rezulin "may effectively suppress evidence" of elevation of enzymes, Pl. Mem. 14 & n.17, the plaintiffs' brief cites Dr. Julie's second declaration: "[S]tudies and articles confirm that Rezulin may suppress transaminase levels and mask this

one indicium of liver injury." Julie (3/18/03) Decl. ¶ 12 (Ex. 336). This statement is highly tentative. Moreover, the studies and articles that Dr. Julie cites in support of the statement show only that Rezulin can depress *baseline* enzyme levels in non-injured animals and patients and in cell cultures of rat kidney cells. They say nothing about whether this effect would persist if the Rezulin caused a liver injury. *See* Caldwell et al. (2001a) (non-injured patients); Caldwell (2001b) (same); Extracts of Mtg. of Austr. Drug Eval. Comm. (Oct. 1-2, 1998) ¶ 2.17.25 (Ex. 359) (rats); Routh et al. (2002) (cultures of rat kidney cells). Dr. Julie's extrapolation from these findings therefore is speculation.

The plaintiffs and Dr. Julie's declaration cite also evidence from Warner-Lambert researchers, but the evidence does not say what the plaintiffs would have it say. Dr. Kan He's two-line email about two patients who died after taking Rezulin but who had normal ALT levels does not give any context or indicate whether there was an elevation of the other three substances. *See* Email from Kan He to Rebecca Boyd (Jan. 19, 1999) (Ex. 365). And the patient with an ALT level of 122 mentioned by Dr. Maddrey in his deposition *did* have an elevated enzyme level – 122 was three times the normal level. *See* Maddrey (7/16/02) Dep. 238-40 (Ex. 290). Additionally, the plaintiffs and Dr. Julie cite two letters from physicians to their colleagues, but one of those letters makes no mention of enzyme levels, *see* Letter from Randall W. Whitcomb (Jan. 4, 1995) (Ex. 376), and the other notes that levels were elevated, *see* Letter from Janet B. McGill to Robert Misbin (March 1, 2000) (Ex. 378).

As for the argument that "[w]here the liver is already significantly damaged . . . or scarred, it will have less healthy cells and, therefore, less transaminases to release," Pl. Mem. 17; *accord* Pl. Facts ¶ 244, the plaintiffs do not even cite expert testimony to that effect. Dr. Bonkovsky's Declaration, which the brief cites, *see* Pl. Mem. 17 n.28, asserts that Rezulin can cause injury without an elevation of ALT but says nothing about a depletion of transaminases. *See* Bonkovsky Decl. ¶¶ 21-24, 29 (Ex. 332). Dr. Julie testified at the hearing "that if there is enough hepatocyte and liver dysfunction and destruction, there may be a diminished hepatic reserve to the point where enzymes are much less likely to spike because of a lack of normal hepatic tissue," Tr. 5/21/03, at 252, but this statement was unsupported and it does not appear in Dr. Julie's declaration. The plaintiffs cite also testimony from physicians to the effect that patients with cirrhosis do not always have elevated enzymes. Pl. Mem. 17 n.28. That testimony, however, says nothing about enzyme levels during any liver injury caused by Rezulin and, more to the point, it does not discuss the physiological theory in support of which the plaintiffs' brief cites it. *See* Julie (7/29/02) Dep. 111 (Ex. 281); Watkins (6/15/01) Dep. 162 (Ex. 306); Maddrey (7/16/02) Dep. 166 (Ex. 290). Finally, the plaintiffs cite a letter from Dr. Watkins to Parke-Davis stating:

> "Rezulin characteristically produces an hepatocellular injury, i.e., elevations in serum alanine aminotransferase (ALT) with normal serum bilirubin early in the course of injury. Jaundice generally occurs only when hepatocellular injury has been severe as indicated by serum ALT > 1,000 IU/L of duration greater than 1 week. The only exception has been in patients caught very late in the course of their illness (when the liver's supply of ALT has been exhausted) or when the patients have preexisting severe cirrhosis." Letter from Paul B. Watkins to Mark

experts in support of their opinion that Rezulin can cause liver injury silently that requires further consideration is that involving apoptosis.

D. Patients Whose Liver Enzymes Were Not Monitored

Plaintiffs' counsel raise the possibility that some people had abnormally elevated liver enzymes while on Rezulin therapy that were not recorded, either because the patient was not tested or was not tested at a time when the enzymes were elevated.[127] The Court recognizes this possibility. But it has no bearing on the present motion, as it does not speak to whether Rezulin *can* cause liver injury through a mechanism that does not result also in elevated enzymes.

V. Law Governing the Admission of Expert Testimony

A. Daubert *and Its Progeny*

The standard governing a district court's determination whether to admit scientific or other expert testimony is familiar. Federal Rule of Evidence 702 provides:

> "If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3)

Caswell (March 1, 1999) (Ex. 404).

This statement does not necessarily accord with the theory at issue. A patient can be an "exception" to the course of injury described in the letter and still exhibit abnormally elevated enzymes. Indeed, Dr. Watkins stated in his own expert report that "I am unaware of even a single documented instance where Rezulin more likely than not caused significant liver injury without causing an elevation in serum ALT." Watkins (10/1/02) Report ¶ 17 (Ex. 331).

127 Pl. Mem. 15-16.

the witness has applied the principles and methods reliably to the facts of the case." This rule incorporates principles established by the Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*[128] The Court there recognized that district judges have a "gatekeeping"[129] role in which they must ensure that "scientific testimony or evidence admitted is not only relevant, but reliable."[130] *Daubert* observed that the relaxation for expert witnesses of the usual requirement of first-hand knowledge presumably "is premised on an assumption that the expert's opinion will have a reliable basis in the knowledge and experience of his discipline."[131] For that reason, a trial judge must "make certain that an expert . . . employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field."[132]

A federal district judge faced with a challenge to the admissibility of expert testimony:

> "must determine at the outset . . . whether the expert is proposing to testify to . . . scientific knowledge that . . . will assist the trier of fact to understand or determine a fact in issue. This entails a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue."[133]

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128 509 U.S. 579 (1993).

129 *Id*. at 597.

130 *Id*. at 589.

131 *Id*. at 592.

132 *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999).

133 *Daubert*, 509 U.S. at 592-93.

These matters are to be determined by a preponderance of proof.[134]

The inquiry is "a flexible one."[135] In *Daubert*, the Supreme Court articulated four pertinent factors while leaving open the possibility of others: (1) whether the expert's theory "can be (and has been) tested;" (2) whether the theory "has been subjected to peer review and publication;" (3) the "known or potential rate of error;" and (4) whether the theory has "widepsread acceptance."[136] Courts have considered other factors as well, including whether an expert's opinion was developed for litigation and whether the expert has accounted adequately for obvious alternative explanations.[137]

In addition, Rule 702's requirement that the proposed testimony "assist the trier of fact to . . . determine a fact in issue" means that the proffered testimony must be "sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute."[138] The *Daubert* decision recognized that this consideration, which has been described as one of "fit," "goes primarily to relevance."[139] A district court therefore is not required "to admit opinion evidence that is connected

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134 *Id*. at 592 n.10.

135 *Id.* at 594.

136 *Id.* at 593-94.

137 *See* FED. R. EVID. 702 advisory committee's note; *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995) (opinion was developed for litigation); *Claar v. Burlington N. R.R.. Co.*, 29 F.3d 499, 502 (9th Cir. 1994) (expert failed to consider other possible causes for plaintiff's injuries).

138 *Daubert*, 509 U.S. at 591 (quoting *United States v. Downing*, 753 F.2d 1224, 1242 (3d Cir. 1985)).

139 *Daubert*, 509 U.S. at 591.

to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."[140]

Thus in *General Electric Co. v. Joiner*,[141] the Supreme Court held that a district court did not abuse its discretion when it excluded the testimony of experts that exposure to polychlorinated biphenyls (PCBs) was likely responsible for the lung cancer of an electrician who was a smoker and had a family history of lung cancer. The Supreme Court found that the animal studies on which the experts relied, which involved exposing infant mice to massive doses of PCBs, "were so dissimilar to the facts presented in this litigation that it was not an abuse of discretion for the District Court to have rejected the experts' reliance on them."[142] The Supreme Court likewise did not take issue with the district court's conclusions that four epidemiological studies were not a reliable basis for the experts' opinions. In two of the four studies, the authors were unwilling to conclude that PCB exposure had caused cancer in the observed workers. The third study did not even involve PCBs, and the subjects in the fourth had been exposed to numerous carcinogens in addition to PCBs.[143]

The Second Circuit's recent case law follows the logic of *Joiner* and *Daubert*. In

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140 *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997); *see also In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 743 (3d Cir. 1994) ("[E]ven if an expert's proposed testimony constitutes scientific knowledge, his or her testimony will be excluded if it is not scientific knowledge *for purposes of the case*. . . . For example, in order for animal studies to be admissible to prove causation in humans, there must be good grounds to extrapolate from animals to humans . . . .").

141 522 U.S. 136 (1997).

142 *Id*. at 144-45.

143 *Id*. at 145-46.

Amorgianos v. National Railroad Passenger Corp.,[144] the Circuit reiterated the familiar principles governing the admissibility of expert testimony and further held that:

> "[t]o warrant admissibility . . . it is critical that an expert's analysis be reliable at every step. . . . In deciding whether a step in an expert's analysis is unreliable, the district court should undertake a rigorous examination of the facts on which the expert relies, the method by which the expert draws an opinion from those facts, and how the expert applies the facts and methods to the case at hand."[145]

In that case the district court was confronted with expert testimony that, among other things, exposure to certain toxic chemicals was a general cause of the type of neuropathy allegedly suffered by the plaintiff bridge painter. The district court "conducted an extremely thorough review of the scientific literature" on which those experts relied.[146] The Circuit found that this review:

> "was certainly within the broad discretion afforded to the district court under *Daubert* and its progeny, and did not impinge upon the jury's function. It is precisely such an undertaking that assures that an expert, when formulating an opinion for use in the courtroom, will employ the same level of intellectual rigor as would be expected in the scientific community."[147]

The Circuit upheld the district court's exclusion of the experts.[148] The district court found that the articles cited by at least one of the experts "fail[ed] to 'fit' the facts of this case, either in terms of the type and duration of exposure, or the type and duration of the observed effects."[149]

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144 303 F.3d 256 (2d Cir. 2002).

145 *Id*. at 267; *accord In re Paoli R.R. Yard PCB Litig.*, 35 F.3d at 743, 745.

146 *Id*. at 269.

147 *Id*.

148 *Id*. at 270.

149 137 F. Supp. 2d 147, 188 (E.D.N.Y. 2001).

It found it significant as well that this expert "prepared his opinion for litigation, rather than as part of his academic research, and he has not seen fit to share his opinion" with the relevant professional community.[150]

The Second Circuit's most recent pronouncement on the admissibility of expert testimony came last year in *Wills v. Amerada Hess Corp.*[151] In that case, the Circuit held that a district court did not abuse its discretion when it excluded an expert report theorizing that a sailor's cancer probably was caused by toxins to which he had been exposed on the defendant's ships. The district court found that the studies on which the expert had relied did not establish a sufficient link between the toxins and the type of cancer because they were done only on animals and found a significant link only when the animals ingested the chemical, which the sailor had not done. The court was dissatisfied also with the expert's failure to account adequately for the possibility that the cancer had been caused by the sailor's smoking and drinking.[152] Finally, the court found that the expert's novel theory of causation – which the expert admitted was "the product of his own 'background experience and reading'"[153] – failed the *Daubert* test because it had not been tested or subjected to peer review, there was no known error rate, and it was not generally accepted.[154]

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150 *Id*.

151 379 F.3d 32 (2d Cir. 2004).

152 *Id*. at 38-39.

153 *Id*. at 49.

154 *Id*. at 39-40, 49.

B. The Daubert *Standards Apply to Opinions About General and Specific Causation*

As discussed earlier, a plaintiff in a toxic tort case must prove both general causation, that is, that the alleged toxin is capable of causing injuries of the kind suffered by the plaintiff, and specific causation, that is, that the alleged toxin caused the particular plaintiff's injuries. The *Daubert* requirements apply alike to expert opinions on general and specific causation. Indeed, since *Daubert* many district courts have excluded expert testimony regarding general causation on grounds quite similar to those proposed here.[155]

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155 *See, e.g.*, *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 182-91 (E.D.N.Y. 2001), *aff'd*, 303 F.3d 256 (2d Cir. 2002) (excluding testimony that exposure to xylene in the amount and for the duration allegedly experienced by plaintiff could cause his alleged symptoms; the "analytical gap" between the experts' conclusions and the conclusions of the studies on which the experts relied was too great, and the experts' opinions were prepared for litigation and not shared with their peers); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1206-1213 (10th Cir. 2002) (upholding decision to exclude, among other things, testimony that Parlodel causes vasoconstriction, hypertension, and ensuing stroke on the grounds that, among other problems, studies on animals and on humans with a particular condition could not be reliably extrapolated, and that arguments based on Parlodel's chemical structure and pharmacological properties were too speculative); *Fabrizi v. Rexall Sundown, Inc.*, No. 01-289, 2004 WL 1202984, at *6-8 (W.D. Pa. June 2, 2004) (M.J.), *Rep & Rec. adopted* June 24, 2004 (excluding testimony of a physician that ingestion of St. John's wort could cause eye cataracts on grounds that *in vitro* studies of animal eye tissue could not be extrapolated to live humans); *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 542, 546-50, 567-72 (W.D. Pa. 2003) (excluding testimony that Parlodel can cause intracerebral hemorrhage ("ICH") because the testimony, which was based on anecdotal case reports, animal studies, other drugs, and studies of patients with pathologies other than ICH, flunked all of the *Daubert* criteria); *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1031-1040 (S.D. Ill. 2001) (excluding testimony that Parlodel can cause ICH because the experts' conclusion "requires too many extrapolations from dissimilar data, too many analytical leaps and involves a loose application of purportedly objective scientific causation standards"); *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1407-11 (D. Or. 1996) (excluding testimony that silicone is capable of causing certain symptoms because the experts were making "too great a leap of faith"; animal studies could not be reliably extrapolated to humans without explanation, case reports were insufficient to prove causation, and studies of crystalline silica were irrelevant because the plaintiffs had not shown that silicone breast implants were associated with the presence of crystalline silica).

VI. Daubert *Analysis of the Proposed Testimony*

A. Testing and Error Rate, Peer-Review, Publication, Widespread Acceptance

The challenged testimony in this case does not satisfy any of the core *Daubert* factors. The theory that Rezulin can cause a liver injury silently never has been tested[156] and necessarily has no error rate. It never has been published or subjected to peer review – aside from an edited version of Dr. Smith's report, which used more tentative language[157] and which he published in a toxicology journal at the suggestion of a member of its editorial board who also is a paid consultant for the

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156 As will be discussed below, to the extent aspects of the theory have been tested, the tests have tended to disprove the hypothesis.

157 As relevant here, the article said:

> "The initial stages of apoptotic injury in a tissue *may therefore be 'silent'* both pathologically, because the apoptotic cells are removed, and clinically, because there will be no rise in serum transaminases and other proteins that are used as markers of tissue injury. . . . The literature to date suggests that TGZ is . . . *potentially able* to damage the liver silently because apoptosis does not cause elevation of liver enzymes in serum . . . ." *Id*. at 682, 683-84 (emphasis added).

The expert reports are more definite, as indeed they would have to be in order to stand any chance of being admissible:

> "The initial stages of apoptotic injury in a tissue *can therefore be 'silent'* both pathologically, because the apoptotic cells are removed, and clinically because there will be no rise in serum transaminases and other proteins that are used as markers of tissue injury. . . . A careful review of all of the literature allows one to conclude to a reasonable degree of scientific certainty that TGZ more likely than not . . . *can* damage the liver 'silently' because apoptosis does not cause elevation of liver enzymes in serum[.]" Smith (9/2/02) Decl. ¶¶ 20, 32 (Ex. 339) (emphasis added).
>
> "[I]t is my expert opinion that TRO induces apoptosis and *can* damage the liver 'silently' during exposure." Smith (3/17/03) Decl. ¶ 9 (Ex. 340) (emphasis added).

plaintiffs in this litigation.[158] It appears to have no acceptance outside this litigation, let alone widespread acceptance.[159]

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158 *See* Martyn T. Smith, *Mechanisms of Troglitazone Hepatotoxicity*, 16 CHEMICAL RESEARCH IN TOXICOLOGY 679 (2003); Tr. 5/20/03, at 128-29, 135-36.

Another reason why the Court does not attribute much significance to the publication of Dr. Smith's report is that the silent liver injury theory is more in the realm of cell biology (insofar as it depends on apoptosis) and hepatology (insofar as it speaks to liver injury and disease) than toxicology. The Court does not consider a toxicology journal's publication of Dr. Smith's otherwise unsupported theories as indicating anything other than that the theories are interesting and worth consideration.

159 The plaintiffs have argued that one sentence in the *Cecil Textbook of Medicine* indicates widespread acceptance of the proposition that Rezulin can cause injury without elevated enzymes. Pl. Reply to Def. Facts ¶ 3.13; *see also* Pl. Facts ¶ 231; Tr. 4/23/03, at 42, 44, 76, 83, 110. The plaintiffs are wrong for at least two reasons.

The relevant statement is:

> "Chronic hepatitis has been associated with an increasing number of drugs, including . . . troglitazone . . . . Although these agents more often cause acute liver injury, prolonged use may occasionally result in a chronic progressive process, leading in some instances to cirrhosis." Nathan M. Bass, *Toxic and Drug-Induced Liver Disease*, *in* CECIL TEXTBOOK OF MEDICINE 779, 781 (Lee Goldman & J. Claude Bennett eds., 21st ed. 2000).

This does not say that a troglitazone-induced injury, whether acute or chronic, would be silent. Under a separate heading, the text goes on to say that "[c]hronic liver injury from some agents increases collagen deposition [i.e. fibrosis], often . . . absent evidence of hepatocellular necrosis or inflammatory response." *Id.* That statement suggests that some drugs can cause liver injury without hepatocellular necrosis, but not that Rezulin is such a drug or that such injury would be silent (the injury could be cholestatic, which is not silent).

The second reason why this passage in the *Cecil Textbook* does not help the plaintiffs is that medical textbooks by their nature are summaries of empirical research and therefore may contain inaccuracies and overgeneralizations. If a statement in a textbook is unsupported by research, the textbook does not buttress the reliability of the expert testimony in question. *See Caraker v. Sandoz Pharms. Corp*., 172 F. Supp. 2d 1046, 1052 (S.D. Ill. 2001) ("[M[edical texts provide no more support than the evidence upon which they rely."); *cf Glastetter v. Novartis Pharms. Corp*., 107 F. Supp. 2d 1015, 1035 n.18 (E.D. Mo. 2000) ("[T]exts and treatises that draw an 'association' between Parlodel and vasoconstriction based upon case reports [do not] make such texts and treatises any more reliable than the case reports on which they rely."), *aff'd*, 252 F.3d 986 (8th Cir. 2001); *Soldo v. Sandoz*

The plaintiffs argue that the research linking Rezulin to apoptosis and apoptosis to injury is part of the established scientific literature.[160] The challenged testimony however, is the opinion that Rezulin is capable of causing a silent liver injury. At issue, in other words, is much more than the independent assertions that Rezulin causes apoptosis in some types of cells under some conditions and that excessive apoptosis can be injurious. It is the extrapolation from the existing literature that never has been tested, peer-reviewed, published, or widely accepted.[161] As the Second Circuit has made clear, "it is critical that an expert's analysis be reliable *at every step* . . . '*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible.'"[162]

B. Independence from Litigation

There is likewise no real dispute that the theory that Rezulin can cause a silent liver injury was developed solely in connection with this litigation. The plaintiffs have come forward with no evidence that Dr. Smith ever proposed this idea publicly before, and Dr. Reed admitted at the

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Pharms. Corp., 244 F. Supp. 2d 434, 542 (W.D. Pa. 2003) (same); *Siharath v. Sandoz Pharms. Corp*., 131 F. Supp. 2d 1347, 1370 (N.D. Ga. 2001) (same). The situation is comparable to a legal treatise making a broad statement that is not supported by the cases it cites. Lawyers are familiar with such inaccuracies. Their occurrence in medical textbooks as well would be unsurprising.

160 Pl. Reply to Def. Facts ¶ 15.1.

161 The plaintiffs argue that the opinions and the research supporting it nonetheless reliably could be used to support the diagnosis of an individual patient because it is accepted practice for scientists and physicians to consider all available information in making a diagnosis or attributing a cause. *Id*. ¶¶ 1.1, 1.2, 14.1. The Court deals with this argument in section VII below.

162 *Amorgianos*, 303 F.3d at 267 (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir. 1994)) (first emphasis added).

evidentiary hearing that he had not presented the theories in his expert report on the possible mechanisms of Rezulin's alleged toxicity in any context other than this litigation.[163]

C. Consideration of Contrary Evidence

A factor that courts have considered in *Daubert* analyses is whether an expert has accounted adequately for obvious alternative explanations. This is appropriate because any theory that fails to explain information that otherwise would tend to cast doubt on that theory is inherently suspect. By the same token, if the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable. Accordingly, courts have excluded expert testimony "where the expert selectively chose his support from the scientific landscape."[164]

In this case, the plaintiffs' experts have ignored a large amount of information that calls many aspects of the silent injury theory into question.

Their reports do not mention that the one study that looked for Rezulin-induced apoptosis in humans failed to find it. Caldwell et al. (2001a) administered Rezulin to human patients

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163 Tr. 5/20/03, at 177-78.

164 *Carnegie Mellon Univ. v. Hoffmann-LaRoche, Inc.*, 55 F. Supp. 2d 1024, 1039 (N.D. Cal. 1999); *accord Lust v. Merrell Dow Pharms, Inc.*, 89 F.3d 594 (9th Cir. 1996) (affirming district's court's exclusion of evidence on grounds, among others, that the expert had "'pick[ed] and chos[en]' from the scientific landscape"); *see also Miller v. Pfizer, Inc.*, 196 F. Supp. 2d 1062, 1086-87 (D. Kan. 2002) ("selective reliance . . . 'is not generally accepted practice' . . . . [O]btaining information from sources that support, refute or are neutral regarding the hypothesis is appropriate to minimize the likelihood of a false conclusion"), *aff'd*, 356 F.3d 1326 (10th Cir. 2004).

and looked for morphological and biochemical evidence of apoptosis but found none.[165]

The expert reports point out that Toyoda et al. (2001) found that Rezulin induced apoptosis in healthy rat hepatocytes. But they do not mention that Kim et al. (2002) – a paper of which Dr. Reed was a coauthor and which he discussed in his declarations – investigated healthy hepatocytes from cynomologus monkeys and found that Rezulin, alone or in combination with the anti-tumor agent TRAIL, failed to induce apoptosis. Rats are much further than monkeys from humans, and Dr. Reed himself regards cells from monkey as a useful alternative to human cells.[166]

The expert reports do not mention that four of the studies on cancer cells – including the Kim et al. (2002) study performed in Dr. Reed's laboratory – compared the effect of troglitazone on the cancer cells to the effect on healthy cells and that, in every such comparison, troglitazone was found to induce apoptosis in the cancer cultures while having no effect on the healthy cells.[167] The expert reports do not mention, in other words, that the reason many researchers were investigating troglitazone's effects on cancer cells and on diseased tissue is that they were actively exploring the

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165 The declaration Dr. Reed submitted after the defendants made the present motion included an explanation for this result that itself seems deficient under the *Daubert* standards. *See* footnote 174 below.

166 *See* Tr. 5/20/03, at 191-93 (Reed cross); Kim et al. (2002), at 22329 ("[H]epatocytes from cynomologus monkeys are a valid surrogate for human hepatocytes where TRAIL-induced apoptosis is concerned."); *see also* Reed (9/9/02) Dep. 668 (Ex. 295) (acknowledging that Dr. Reed would use monkey hepatocytes as an alternative to human hepatocytes).

167 *See* Kim et al. (2002) (troglitazone plus TRAIL not toxic to normal hepatocytes, endothelial cells, a type of blood cell, and bone marrow); Elstner et al. (1998) (Rezulin plus hypothesized anti-tumor agent induced apoptosis in breast cancer but neither substance alone or in combination produced this effect in healthy breast epithelial cells); Harris & Phipps (2002) (Rezulin induced apoptosis in malignant T cells but not healthy ones); Kubota et al. (1998) (troglitazone produced necrosis in malignant but not normal prostate tissue).

possibility that the drug could be an effective therapy for killing or preventing the proliferation of malignant tissue without harming healthy cells.

The expert reports do not discuss the fact that the same researchers who found that troglitazone affected the mitochondria in the cells of live humans, immortalized liver cells, and liver cancer cells either observed no evidence at all of apoptosis or other cell death[168] or, if they did observe cell death, (i) observed it at concentrations higher than the concentrations required to affect the mitochondria, and (ii) did not specify whether the mechanism was apoptosis.[169] The expert reports did not discuss the fact that Shishido et al. (2003), a study performed on immortalized human liver cells, looked for but could not find cytochrome c, considered a sign of apoptosis, and believed this absence "suggest[ed] no clear involvement of mitochondria-mediated apoptosis in this *in vitro* system as previously reported."[170] The expert reports saw fit to omit that, while Haskins et al. (2001) did find that troglitazone affected the mitochondria in liver cells derived from one diabetic patient, these researchers failed to see this result in the cells derived from another diabetic patient.

In other words, the scientists have discussed only the evidence that they believed would advance the plaintiffs' position. Their reports cannot be said to reflect "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field."[171]

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168 *See* Caldwell et al. (2001a) (live humans); Shishido et al. (2003) (immortalized human liver cells).

169 *See* Tirmenstein et al. (2002) (liver cancer cells).

170 Shishido et al. (2003), at 140. Note that "as previously reported" is a reference to Koga et al. (2001), which is discussed in footnote 99.

171 *Kumho Tire Co.*, 526 U.S. at 152 (1999).

D. "Fit" and the "Analytical Gap"

A crucial consideration in evaluating the admissibility of expert testimony is whether the conclusions flow reliably from the premises. As the Supreme Court has explained, "[a] court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."[172] Or as Judge Becker has explained for the Third Circuit: "[e]ven if an expert's proposed testimony constitutes scientific knowledge, his or her testimony will be excluded if it is not scientific knowledge *for purposes of the case*."[173] This consideration is bound up with the relevancy requirement described in *Daubert* as one of "fit."

The analytical gap between the research and the conclusions the experts would draw is independently sufficient to warrant exclusion of the testimony in question. The plaintiffs have no evidence for the final link in their causal chain, and they extrapolate from the earlier links in ways the Court finds unreliable.

1. The Experts Have No Evidence for the Crucial Link in Their Causal Chain

The experts have no evidence to carry them all the way down their causal chain to silent liver injury.

It is worth bearing in mind that some level of apoptosis is entirely normal and occurs all the time in healthy tissue. Drs. Reed and Smith admitted that they have no information on whether therapeutic doses of Rezulin, even assuming they can cause additional levels of apoptosis

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172 *Joiner*, 522 U.S. at 146.

173 *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 743 (3d Cir.1994).

beyond the normal baseline, can do so to a clinically relevant extent.

Furthermore, both sides' experts and the literature agree that when an insult producing apoptosis is sufficiently serious, the injury or impairment will not be silent. Thus the question is not just whether Rezulin can cause apoptosis to occur at levels sufficient to cause injury or impairment, but whether it can do so and remain silent. The plaintiffs' experts have offered no evidence that this is possible. Indeed, *nothing* in the challenged expert reports gives *any* indication about the actual capacity of phagocytes (the "clean-up" cells) to absorb the end products of apoptosis – the precondition to the injury's hypothesized silence.

2. The Experts Have Failed To Link the Studies on Mitochondria and the BSEP into Their Causal Chain

Similarly, the studies on mitochondria have no connection to Rezulin-induced apoptosis. Dr. Smith would opine that (a) Rezulin has been shown to affect the structure and function of the mitochondria, and (b) apoptosis has been shown to involve changes to the mitochondria, and therefore (c) Rezulin can produce apoptosis. This is speculative, and it confuses association with causation. Dr. Smith's reasoning is logically equivalent to saying that (a) every time John gets hungry he eats, and (b) John eats whenever he goes to a restaurant, therefore (c) every time John gets hungry, he goes to a restaurant. There are of course plenty of times when John gets hungry and eats at home.

So too here. There is not simply the possibility that Rezulin changes the mitochondria without producing apoptosis. There are empirical demonstrations of this in the studies of Caldwell

et al. (2001a),[174] Shishido et al. (2003),[175] and Tirmenstein et al. (2002)[176] performed, respectively, on live humans, immortalized human liver cells, and liver cancer cells.[177] The plaintiffs' experts must have some reliable basis for asserting that Rezulin-induced mitochondrial abnormalities lead specifically to apoptosis, otherwise the mitochondria research does nothing to help them survive this motion. The plaintiffs' experts have no such basis.

Nor is Dr. Smith's theory rendered reliable by the fact that he, and some of the articles he cites, assert that a change in mitochondrial membrane function itself is an initial cause of, and not

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174 Dr. Reed says that Caldwell et al. (2001a) took the biopsies too late to measure any apoptosis. *See* Reed (2/25/03) Decl. 13 (Ex. 338) ("Apoptotic cells are rapidly cleared by phagocytosis, and thus if one samples tissues too late, the cells are already gone, and the evidence is lost."). But those researchers say only that they took the biopsies "at the end of treatment." Caldwell et al. (2001a), at 520. Dr. Reed and the plaintiffs have given the court no reason to believe that biopsies – the positive results of which the *plaintiffs* (using Dr. Julie's report, *see* footnote 92 above) say are indeed evidence of Rezulin-induced apoptosis – would not detect an apoptotic injury. Indeed, one of the plaintiffs' experts has stated: "Hepatologists generally agree that liver biopsy is the definitive medical test for the characterization of the nature, severity, and progression of liver disease." Bonkosvky Decl. ¶ 21 (Ex. 332).

175 As discussed elsewhere in this opinion, Shishido et al. (2003) specifically chose a concentration that they believed would avoid apoptosis, and found that despite the effect on mitochondria, Rezulin did not produce the biochemical incidents of apoptosis.

176 As discussed above, Tirmenstein et al. (2003) reported that troglitazone causes cell death, but they only observed this effect at concentrations higher than the ones required to affect the mitochondria. Furthermore, the Tirmenstein authors do not specify whether the cell death occurred via apoptosis or necrosis.

177 Finally, there is Haskins et al. (2001), which did not measure apoptosis at all, but which did find that troglitazone at certain concentrations affects the mitochondria of rat cells. The concentration required to induce the effect, however (approximately 200 μM and above) was close to or greater than the concentration that was found to produce a total depletion of ATP in the cells. *See* Haskins et al. (2001) (Figs. 2, 6A, 7). It is undisputed that apoptosis requires ATP. Smith (9/2/02) Decl. ¶ 27 (Ex. 339); Tr. 5/20/03, at 77-78, 107 (Smith direct and cross), 157 (Reed direct). Thus any effect on the mitochondria in the rat cells could not logically have caused apoptosis in those cells. The experts do not address this difficulty.

just a phenomenon associated with, apoptosis. The fact that there is compelling evidence (which he ignores) in the very studies that he and Dr. Reed cite to the effect that human liver cells – normal, immortalized, and cancerous – can sustain mitochondrial damage without shriveling up and dying undermines what the plaintiffs' counsel have described as Dr. Smith's "one plus one equals two"[178] argument.

The BSEP research suffers from the same basic difficulty discussed above. That is, while there are studies to suggest that Rezulin, through a mechanism involving the BSEP, can produce cholestatic injury and that cholestatic injury is associated with apoptosis, there is no reason to believe that any apoptosis caused by BSEP malfunction would be silent. The cholestatic injury that Rezulin produced in rats in the two Funk et al. studies was manifested by the presence in the rats' blood of products closely associated with bilirubin.

For apoptosis associated with cholestasis to be silent, surrounding phagocytes would have to absorb the dying bile salt-filled cells. Can they really do this? The very toxicity to cells of bile and related compounds – this is to be contrasted with ALT and AST – is a starting point of the research on the BSEP and cholestasis. Dr. Smith offers no help in resolving this paradox, and therefore no reason to believe that inhibition of the BSEP by Rezulin could produce a silent injury.

3. The Research on Apoptosis in Cell Cultures Does Not "Fit" the Opinion at Issue

The preceding discussion shows that the most that can be said for the research cited by the experts, to the extent it is relevant at all, is that it shows that at certain concentrations, Rezulin causes apoptosis in the hepatocytes of rats (but not monkeys), in human liver cancer cells, in

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[178] Tr. 4/23/03, at 72.

cancerous cells of other organs (but, so far as the data presented to the Court indicate, not in healthy cells from those organs), and in non-cancerous disease tissue.[179] The plaintiffs argue that the experts can extrapolate reliably from *in vitro* results to draw conclusions about the effect of Rezulin in humans.

Caution always must be used in extrapolating results in tissue culture to effects in live humans.[180] As explained in the *Reference Manual on Scientific Evidence*:

> "Thousands of in vitro toxicological tests have been described in the scientific literature. . . . There are short-term in vitro tests for just about every physiological response and every organ system . . . . Relatively few of these tests have been validated by replication in many different laboratories or by comparison with outcomes in animal studies to determine if they are predictive of whole-animal or human toxicity."[181]

In assessing the reliability of an extrapolation from *in vitro* results to effects in live humans, two crucial considerations are the type of cell on which the *in vitro* experiment was performed and the

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179 The potentially relevant studies are the ones discussed in IV.B.1.a above:

1. Toyoda et al. (2001), which found that Rezulin causes apoptosis in rat hepatocytes;
2. The quartet of studies – Bae and Song (2003), Toyoda et al. (2002), Yoshizawa et al. (2002), and Yamamoto et al. (2001) – that found that Rezulin causes apoptosis in liver cancer cells;
3. The studies on cancer cells of other organs;
4. The studies on other disease tissue.

180 *See, e.g.*, Reed (7/1/02) Dep. 109 (Ex. 293) ("Q. If you see an effect in a cell culture, would that be a sufficient basis to conclude that that, in fact, is indeed what happens in humans? A. No. Q. If that was done, would that be good science? A. No."); Day (4/12/01) Dep. 242 (Ex. 272) ("Q. You indicated to me that the in vitro data . . . did not involve patients, and therefore cannot be extrapolated? A. It's difficult to know how to use that data precisely. Q. And the reason that pharmaceutical companies and medical researchers do tests in human patients is because you can't reliably always take data from cell cultures and say this is what is going to happen in the human body? A. If only we could.").

181 *Reference Guide on Toxicology*, *supra*, at 410.

dose to which the cells were exposed.[182]

a. Types of Cells

In the cited studies, the cells in which Rezulin was found to produce apoptosis were not normal human liver cells. They were either healthy liver cells of rats, cancerous human liver cells, and cancerous or otherwise abnormal cells from other human organs. This fact is of substantial significance. In light of the explanations of the plaintiffs' experts and the concessions of the plaintiffs' counsel, almost none of these studies appears to be a reliable basis for extrapolating to the liver of a living human.

To begin with, Dr. Smith described at the hearing a "hierarchy" of relevance of experiments on different kinds of cells.[183] At the top of the hierarchy is human hepatocytes. Next is "immortalized" hepatocytes, which Dr. Smith rates "about equivalent" to "rat hepatocytes or any of the animal liver cells."[184] The third level is "liver tumor cells, such as hepatoma cell lines. And the fourth part of the hierarchy would be non-target tissue cells."[185] The suggestion is that extrapolation becomes less and less appropriate as one proceeds down the hierarchy.

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182 *See id*. ("Criteria of reliability for an in vitro test include . . . whether the test is predictive of in vivo outcomes *related to the same cell or target organ system*.") (emphasis added); *id*. at 422 ("The major barrier to use of in vitro results is the frequent inability to relate doses that cause cellular toxicity to doses that cause whole-animal toxicity."); Tr. 5/20/03, at 57-59 (Smith direct) ("[W]hen you are extrapolating you have to bear various things in mind. First of all, is the test system [i.e. the type of culture] well-established? . . . The doses that cause cellular toxicity, are these likely to be achievable in human patients?").

183 Tr. 5/20/03, at 59.

184 *Id*.

185 *Id*.

In fact, it is on the basis of this testimony that the plaintiffs' counsel have argued that Rezulin's pattern of harming malignant but not normal tissue from various organs does not detract from their hypothesis that Rezulin is toxic to the (non-cancerous) liver. In their proposed findings of fact, the defendants pointed out that in the body of science before the Court, every time the effects of Rezulin on cancer cells were compared with the effects on normal cells, Rezulin killed the cancer cells without damaging the normal ones.[186] The plaintiffs' response, for each of these studies, is some form of the statement that "[t]he experiment did not concern liver cells and is therefore of limited relevance to troglitazone hepatotoxicity."[187] Indeed, the plaintiffs make a similar statement in connection with other studies performed on non-liver cells.[188]

The plaintiffs thus effectively have abandoned all of the studies on non-liver cells as a basis for their experts' opinions. Accordingly, the Court is convinced that most of the *in vitro* studies upon which the plaintiffs' experts initially relied do not support a reliable extrapolation to the opinion that Rezulin can cause a silent liver injury in humans.

Furthermore, the Court does not regard the four cited studies in which troglitazone produced apoptosis in human liver cancer cells as a reliable basis for predicting the drug's effect on non-cancerous human livers. The plaintiffs and their experts have ignored the evidence that Rezulin

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186 *See* Def. Proposed Findings of Fact ¶¶ 8.2 ("Def. Facts").

187 *See* Pl. Reply to Def. Facts ¶¶ 8.2.3 – 8.2.9.

188 *See id*. 8.3(a) (in response to the defendants' statement that certain studies cited by the plaintiffs' experts "investigated cells from tissues other than liver": "Admit. . . . The opinions expressed by Plaintiffs' experts at the hearing on this matter related to hepatocytes. Dr. Smith testified that non-target tissue cells (i.e., non-liver cells) are at the bottom of the hierarchy of importance in analyzing troglitazone hepatotoxicity.").

does *not* have an apoptotic effect on non-cancerous monkey liver cells and failed to deal with the fact that cancer cells – in the four studies cited to this Court that compared them with healthy cells from the same organ – respond to troglitazone in ways that healthy cells do not. And it is undisputed that cancer cells are abnormal precisely in that their mechanisms of cell growth and death have been disturbed.[189] Indeed, Dr. Smith himself ranked cancerous liver cells as third out of fourth in his hierarchy of relevance.

When all of the studies involving human liver tumor cells and cells from other organs are stripped away, what is left is the Toyoda et al. (2001) study, which investigated rat hepatocytes and is considered below.

b. Dose

It is a fundamental principle of toxicology, as Dr. Smith explained at the hearing, that "the dose makes the poison."[190] Consequently, if the doses at which Rezulin was observed to be toxic to cultured cells are not achieved in the liver *in vivo*, extrapolation from the *in vitro* experiments is

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189 Dr. Day, one of the plaintiffs' experts, explained:

> "The drawbacks with working on cell lines are . . . that this is a malignant cell line that you have picked because it grows forever in the dish and you can study it. It obviously isn't a normal hepatocyte. . . . There is always the worry when you have [liver cancer cell line] work, what does this really mean for a normal healthy hepatocyte? And I think the best laboratory workers in the field tend to develop . . . all their mistakes, if you like, on [the cancer cell line] and produce their hypotheses . . ., but then they try and get hold of some [non-cancerous] hepatocytes and show, even if it is just one or two experiments, that what they are trying to say is so important for the liver based on cancer cell work . . . is actually applicable to the primary cell line." Day (11/26/02) Dep. 173 (Ex. 273).

190 Tr. 5/20/03, at 17; *accord* Tr. 5/21/03, at 342 (Chojkier cross).

not reliable.[191] In light of the preceding discussion, the only *in vitro* study that the Court finds it necessary to consider further is Toyoda et al. (2001), which investigated rat hepatocytes.[192] Thus the question is whether the doses to which the cells in that study were exposed are comparable to those to which cells in the liver of a living human are exposed.

Dose is a function both of concentration of a toxin and of time of exposure.[193] Toyoda et al. (2001) found that troglitazone at concentrations of 15 μM and above killed most of the rat hepatocytes within 20 hours. But that result obtained only in the absence of albumin, a protein to which Rezulin is more than 99 percent bound in human blood.[194] The binding to albumin means that the molecules of troglitazone are not as free to interact with other substances. Results obtained in the absence of albumin therefore cannot readily be generalized or extrapolated to a living human.[195]

Toyoda et al. (2001) itself demonstrates the significance of the presence of albumin. When those researchers added a 2 percent solution of bovine serum albumin to the cells, the same

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191 Tr. 5/20/03, at 57-58 (Smith direct); Tr. 5/21/03, at 342 (Chojkier cross).

192 It is unnecessary to discuss individually the doses administered in the many other studies cited by the plaintiffs' experts in light of the Court's finding that extrapolation from those studies is unreliable for reasons discussed elsewhere in this opinion. Nevertheless, the points made below apply to many of these studies because they were performed with high concentrations of Rezulin and without albumin.

193 Tr. 5/20/03, at 27-28 (Smith direct); Tr. 5/21/03, at 342 (Chojkier cross).

194 Kawai et al. (1997), at 362; Izumi et al. (1996), at 1635; Smith (9/2/02) Decl. ¶ 13 (Ex. 339); Tr. 5/20/03, at 31, 46 (Smith direct).

The plaintiffs' counsel have tried to dispute this point, *see* Pl. Reply to Def. Facts ¶ 13.3.1(c), but the argument contradicts even their own expert's testimony.

195 *See, e.g.*, Day (11/26/02) Dep. 182-83 (Ex. 273).

15 μM concentration of troglitazone that was otherwise so toxic to the cells produced virtually no effect after 24 hours. Even a 100 μM solution of troglitazone destroyed less than 20 percent of the cells, and a 50 μM solution destroyed approximately 5 percent.[196] In human blood plasma, the concentration of albumin is 4 percent,[197] or double the maximum used in the Toyoda et al. (2001) study. The question raised by the Toyoda et al. (2001) results therefore is whether the concentrations at which troglitazone produced apoptosis in the presence of albumin *in vitro* are comparable to the concentrations of troglitazone achieved *in vivo* in therapeutic settings.

When a patient was taking prescribed doses of Rezulin, the average maximum concentration in the blood plasma was determined to be 2.0 to 6.3 μM, depending on the dosage,[198] a finding substantially adopted by experts on both sides.[199] The defendants argue that the concentration in the liver of a patient taking Rezulin is approximately equal to that in the blood plasma,[200] which is a small fraction of the concentrations of troglitazone found to be toxic in the Toyoda et al. (2001) study.

The plaintiffs' experts contend that the concentration of Rezulin inside a patient's

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196 These figures are approximations based on a graph (Figure 6) in the Toyoda et al. (2001) paper.

197 *E.g.*, Tr. 5/21/03, at 209 (Reed cross).

198 *See* Loi et al. (1999a).

199 *See* Tr. 5/20/03, at 119 (Smith cross); Reed (8/30/02) Report ¶ 16 (Ex. 337); Pl. Mem. 43 n.110; Tr. 5/21/03, at 286-87 (Chojkier direct).

200 *E.g.*, Def. Facts ¶ 13.3.

liver actually is much higher – 50 to 80 μM, according to Dr. Smith.[201] At the evidentiary hearing, Dr. Smith said the disparity between this level and the concentration found in the bloodstream is attributable to hepatic first-pass uptake, which is the liver's absorption of certain substances from the bloodstream right after they have left the gut.[202] Furthermore, the plaintiffs' experts have cited research that they say corroborates this range.[203]

Before examining Dr. Smith's analysis, the Court pauses to point out several major difficulties with extrapolation from the published literature. The concentration of troglitazone discussed in Toyoda et al. (2001) is the concentration in the *medium that surrounds the cells*, not the concentration *inside the liver cells*. However, Kawai et al. (1997), the lone published study that found that the concentration of troglitazone in the liver is higher than in the plasma,[204] sought to

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201 Tr. 5/21/03, at 37.

Dr. Reed in his initial expert witness report stated that "[t]he concentration of TGZ that is reached in the liver of humans taking this drug is unknown," but "one could infer that the expected liver concentration would be 10-12 times" the amount in the blood plasma, or "approximately 36 to 80 μM." Reed (8/30/02) Decl. ¶ 16 (Ex. 337). Dr. Reed's inference is based on an extrapolation from an unpublished finding by Parke-Davis reported in Sahi et al. (2000) that troglitazone concentrations are 10 to 12 times greater in the livers of rats than in their blood plasma. Since the concentration in the human blood plasma is believed to be on average 3.6 to 6.3 μM (this range excludes the lowest dosage administered in Loi et al. (1999a)), Dr. Reed multiplied that range by 10 to 12 to arrive at his estimate.

202 Tr. 5/20/03, at 28-37.

203 Drs. Smith and Reed have cited Haskins et al. (2001), Toyoda et al. (2001), Yamamoto et al. (2001), Sahi et al. (2000), Kawai et al. (1997), and internal research performed at Parke-Davis (*see* Memorandum from Kan He to Thomas Woolf et al. 4 (March 11, 1999) (Ex. 367)). *See* Reed (8/30/02) Decl. ¶ 16 (Ex. 337); Smith (9/2/02) Decl. ¶ 26 (Ex. 339); Tr. 5/20/03, at 38-39.

204 Of the other published studies cited in the preceding footnote, Haskins et al. (2001) cites nothing, Toyoda et al. (2001) cites Kawai et al. (1997), Yamamoto et al. (2001) cites Sahi et al. (2000), and Sahi et al. (2000) cites a "personal communication" from a Parke-Davis

measure the concentration in the entire liver tissue without distinguishing between the concentrations inside and outside the cells.[205]

These two concentrations are not interchangeable. The plasma membrane is a selective barrier. Indeed, it is the cell's ability to maintain internal conditions that differ from those outside that makes all life possible.[206] As one of the defense experts has explained:

> "Intact cells have a complex membrane separating the *intracellular* contents from the outside medium or blood. The degree to which a substance in the *extracellular* medium traverses the cell membrane is a complex function of many factors. . . . It is thus grossly incorrect to adopt an *intracellular* concentration, even if correct, and apply that to phenomena observed at a specific *extracellular* concentration."[207]

Furthermore, it is unknown whether any toxicity due to troglitazone is a function of its presence outside the plasma membrane of the cell (where it may interact with certain proteins embedded in the membrane) or inside the cell (where it can interact with compounds in the cytoplasm).

Another difficulty is that the concentrations measured in Kawai et al. (1997) actually encompassed not just the pure troglitazone molecule, but the various related molecules, known as metabolites, that result from biochemical breakdown processes inside the cell.[208] Dr. Smith could

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scientist.

205 There is no indication that other Parke-Davis research referenced in these proceedings made such a distinction, either.

206 *See, e.g.*, BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 11 (4th ed. 2002) ("Without a plasma membrane, the cell could not maintain its integrity as a coordinated chemical system.").

207 Brent Decl. ¶ 25 (Ex. 317).

208 Kawai et al. (1997) used a technique known as radioactive labeling. If a molecule of troglitazone contains a labeled carbon atom, the molecule of metabolite to which the troglitazone is converted will bear that label so long as the metabolite contains the same

give little information the extent to which these metabolites are toxic.[209] In consequence, the concentrations observed by Kawai et al. (1997) may overstate the relevant concentrations by aggregating troglitazone and metabolites that may have different properties.

Thus, although it may be true that troglitazone and its metabolites accumulate in the liver, there is still no basis for the assertion that it is clinically realistic to expose cells in culture to *extracellular* concentrations comparable to the *whole-tissue* concentrations alleged by Drs. Smith and Reed. The question, contrary to what the plaintiffs and their experts have implied, is not whether the concentrations used in Toyoda et al. (2001) match the combined concentration of troglitazone and its metabolites across the entire liver; rather, it is whether the concentrations of troglitazone used in Toyoda et al. (2001) match the concentrations of troglitazone to which the *outside* of the cells in

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carbon atom that was in the parent molecule. The experimenters, in measuring total radioactivity, thus were measuring the combined quantities of troglitazone and its metabolites. *See* PARKE-DAVIS PHARM. RESEARCH DIV., METABOLISM OF CI-991: III. DISTRIBUTION IN RAT TISSUES iii (Research Report No. RR 764-01690, July 1, 1991) (Ex. 216); Tr. 5/20/01, at 40-41, 122 (Smith).

209 Dr. Smith testified as follows:

> "The Court: . . . Now talk to me about the dose of troglitazone-sulphate [a metabolite of troglitazone] at which toxicity is observed in relation to the dose of troglitazone itself. . . .
> "The Witness: Well, troglitazone-sulphate is actually a better inhibitor of the bile salt export pump than troglitazone itself. . . . So the troglitazone-sulphate is five times more potent as an inhibitor of the bile salt export pump than the [parent troglitazone compound]. . . .
> . . .
> "The Court: [I]s [inhibition of the BSEP] the only mechanism that you rely on for characterizing troglitazone as toxic?
> "The Witness: No.
> . . .
> "The Court: Would you compare now apples to apples, the toxicity at given dose levels of troglitazone-sulphate and troglitazone?
> "The Witness: I would have to look at the literature . . . . I have not done a calculation of that particular ratio." Tr. 5/20/03, at 44-45.

patients actually were exposed. Even putting this point aside, however, there are independent difficulties in Dr. Smith's projection of the concentration of Rezulin in the liver based on absorption on the "first pass."

Dr. Smith started with the premise that Rezulin's absolute "bioavailability" – the fraction of the ingested drug that is absorbed from the gut instead of remaining there[210] – is 50 to 70 percent. In other words, if a patient takes 600 milligrams (mg) of Rezulin, 300 to 420 mg will be absorbed by the body.[211] The Court notes that the 50 percent figure is comparable to, if on the high end of, published estimates.[212] The 70 percent figure is based on the premise that food increases bioavailability.[213]

Dr. Smith next stated that 43 percent of that amount (i.e. 129 to 180.6 mg) will be absorbed directly by the liver on the first pass from the gut.[214] He cited Izumi et al. (1996) for that figure, but the study does not support it. In fact, Izumi et al. (1996) assumed what the plaintiffs dispute, which is that "the concentrations of unbound drug in venous blood and liver are equal."[215] Nevertheless, using the molecular weight of troglitazone (441 grams/mole) and assumptions about

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210 *See* Michele A. Medinsky & John L. Valentine, *Toxicokinetics*, *in* CASARETT & DOULL'S, *supra*, at 225, 230.

211 Tr. 5/20/03, at 32.

212 *See* Loi et al. (1999a), at 923 (43.5%); Loi et al. (1999b), at 93 (40-50%); Izumi et al. (1996), at 1638 (39.5%).

213 Tr. 5/20/03, at 32.

214 *Id*.

215 Izumi et al. (1996), at 1638.

the mass of the liver (1500 grams) and its density (1 gram / 1.08 milliliters), Dr. Smith converted the 129 to 180.6 mg to a concentration range: 180.5 to 252.8 μM.[216]

But this number is meaningless.[217] Dr. Smith himself explained that such a concentration would obtain only if all of the Rezulin absorbed by the liver on the first pass were absorbed at once, which it is not, rather than over time.[218] Thus, Dr. Smith said, "If you do a toxicokinetics model of troglitazone it predicts the concentration of troglitazone in the liver will be 50 to 80 micromolar after a therapeutic concentration . . . ."[219]

The plaintiffs have failed to establish any reliable basis for the 50 to 80 μM range. Dr. Smith gave no information on how he reached that number. While he methodically explained the calculations and assumptions that produced the range 180.5 to 252.8 μM, he simply uttered "toxicokinetic modeling" before producing the range of 50 to 80 μM. He provided no information concerning the structure of the model or the data and assumptions used in producing the claimed result.

Moreover, even if Dr. Smith's assertion on this point were accepted, the Court could not accept the figure as reliable. For one thing, it is based on the premise that 43 percent of the absorbed fraction of troglitazone is absorbed directly by the liver on the "first pass," a number that

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216 Tr. 5/20/03, at 33-35.

217 Also meaningless is Dr. Smith's and the plaintiffs' counsels' statement that if the liver weighed much less – say, 825 grams – as some patients' livers do, then the total dose could be as high as 459.6 μM. Tr. 5/20/03, at 36.

218 Tr. 5/20/03, at 34, 36.

219 *Id*. at 36-37.

the Court could not find in the only study that Dr. Smith cited for it. And there is still the problem that Dr. Smith failed to explain how the tissue-wide concentrations he postulates can be used to relate (a) the extracellular concentrations to which cells actually were exposed in patients taking Rezulin to (b) the concentrations used in Toyoda et al. (2001).

In spite of all of this, even if it were accepted that the concentration of troglitazone in the liver is 50 to 80 μM, and even if the failure to distinguish between intracellular and extracellular concentration were overlooked, there would be another reason why extrapolation from the Toyoda et al. (2001) study cannot be said to be reliable. The experts have provided no information on the distribution of troglitazone in the liver. Drs. Smith, Reed, and Julie agree that Rezulin is *not* distributed homogeneously in the liver,[220] but they cannot say how it *is* distributed.[221]

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220 *See* Tr. 5/20/03, at 52, 139 (Smith); Tr. 5/21/03, at 228-30 (Reed), 259 (Julie).

221 The following exchange occurred during Dr. Smith's testimony:

> "The Court: Is there any data at all that indicate on an empirical basis how much of the liver receives the sorts of doses you were talking about this morning as being indicative of cellular injury?
> "The Witness: I don't think there is any empirical data at all . . . . [W]e can't do that measurement.
> "The Court: . . . So conceivably, . . . assuming you are correct for all the reasons you gave this morning that there are at least some cells in the liver in which the dosage can reach levels that in vitro have been identified as toxic, it is possible that the proportion of the cells that reach those levels is extremely small or extremely large, right?
> "The Witness: Sure.
> "The Court: We just don't know.
> "The Witness: We don't know.
> "The Court: Are you expressing any opinions on that proportion?
> "The Witness: No, I am not, your Honor." Tr. 5/20/03, at 139-40.

See also id. at 140-41, 147-50 (Smith); Tr. 5/21/03, at 230 (Reed), 259 (Julie) ("I think [the Court's] point about heterogeneity is a good one and I think that there is going to be some variability amongst the different cell populations . . . and that stuff has not been

That is, they have no information on the percentage of cells that would be exposed to the concentrations that they assert are toxic. The drug may concentrate in discrete pockets, perhaps close to the portal vein,[222] causing localized damage but leaving the rest of the organ unharmed and consequently causing no clinically significant effect. The plaintiffs' experts have no answer to this difficulty.

The Court finds that extrapolation from the results of Toyoda et al. (2001) to the livers of patients who took Rezulin is unwarranted. The Court cannot and does not say that Drs. Smith and Reed are wrong or that the defendants' experts are right. Rather, it is not satisfied that there is a reliable basis for an extrapolation from the results of an *in vitro* experiment that used troglitazone at a concentration of 50 or 100 μM with a 2 percent solution of albumin to clinical effects in a patient taking Rezulin. Similar statements could be made about other studies relied on by the experts, but the Court finds it unnecessary to discuss the specifics of those studies.[223]

VII. The Plaintiffs' Argument Concerning Differential Diagnosis

The plaintiffs attempt to get around all of these problems by arguing that the testimony in question could be used to support opinion testimony regarding causation based on the clinical process of elimination known as differential diagnosis.[224]

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determined.").

222 *See* Tr. 5/20/03, at 149-50.

223 *See* footnote 192 above.

224 Courts have come to use the term "differential diagnosis" differently from practicing physicians. In clinical medicine, "differential diagnosis" describes "the process of determining which of several *diseases* is causing a patient's *symptoms*." *Reference Guide*

The Federal Judicial Center's *Reference Manual on Scientific Evidence* has explained differential diagnosis this way:

> "[T]he physician determines which of two or more diseases with similar clinical findings is the one that the patient is suffering from. The physician does this by developing a list of all of the possible diseases that could produce the observed signs and symptoms, and then comparing the expected clinical findings for each with those exhibited by the patient."[225]

The plaintiffs argue that the opinions about silent liver injury are admissible because they are based on what they call a "plausible mechanism."[226] The plaintiffs' position is that a physician faced with a patient who took Rezulin and experienced silent liver injury could attribute that injury to Rezulin by performing a differential diagnosis that takes that "plausible mechanism" into account.[227] But the plaintiffs have underestimated their burden under *Daubert.*

A physician attempting to establish a causal relationship between exposure to a substance and a particular patient's illness must "demonstrate that the medical and scientific literature provides evidence that in some circumstances the exposure under consideration can cause the outcome under consideration. This step is synonymous with establishment of general

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on Medical Testimony, *supra*, at 443. Expert witnesses and courts, however, frequently use the term "to describe the process by which causes of the patient's condition are identified, particularly causes external to the patient." *Id*. at 443-44. On the whole, the plaintiffs' counsel and their experts have used the term in the latter way.

225 *Id*. at 463.

226 Tr. 4/23/03, at 91.

227 *See generally* Pl. Mem. 18-23; Pl. Facts ¶¶ 1-37; Tr. 4/23/03, at 90-92; Tr. 5/21/03, at 232-68 (Julie direct); Julie (3/18/03) Decl. ¶¶ 2-5, 18 (Ex. 336).

causation."[228] In other words, the determination of cause in an individual case, or differential diagnosis as that term has been used by courts, "does not 'speak to the issue of general causation. [It] assumes that general causation has been proven for the list of possible causes' that it rules in and out in coming to a conclusion."[229] As one court has explained:

> "the final, suspected 'cause' remaining after this process of elimination must actually be *capable* of causing the injury. . . . And, of course, expert opinion on this issue of 'general causation' must be derived from scientifically valid methodology."[230]

A physician thus may not link any particular patient's injury to Rezulin unless there is some reliable basis for the opinion that therapeutic doses of Rezulin can cause such an injury.

The Court is mindful that two district judges in this Circuit seem to have come to a different view, stating, with reference to the Second Circuit's decision in *McCullock v. H.B. Fuller*

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228 *Reference Guide on Medical Testimony*, *supra*, at 469.

229 *In re Rezulin Prods. Liab. Litig.*, No. 00 Civ. 2843, 2004 WL 2884327, at *4 (S.D.N.Y. Dec. 10, 2004) (quoting *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1413 (D. Or. 1996)); *see also Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 989 (8th Cir. 2001) (affirming district court's exclusion of plaintiff's experts because they lacked a proper basis for "ruling in" a drug as a potential cause of alleged injury); *Black v. Food Lion, Inc.*, 171 F.3d 308, 313-14 (5th Cir. 1999) ("Dr. Reyna's use of a general methodology cannot vindicate a conclusion for which there is no underlying medical support."); *Hollander v. Sandoz Pharms. Corp.,* 289 F.3d 1193, 1209-11 (10th Cir. 2002) (affirming exclusion of opinion based on differential diagnosis offered to prove general causation); *Soldo v. Sandoz Pharms. Corp.,* 244 F. Supp.2d 434, 516 (W.D. Pa. 2003) ("differential diagnosis is not a reliable methodology for determining *general* causation"); *In re Breast Implant Litig.*, 11 F. Supp.2d 1217, 1229-30 (D. Colo. 1998) (differential diagnosis not reliable as to general causation).

230 *Cavallo v. Star Enter.*, 892 F. Supp. 756, 771 (E.D. Va. 1995), *aff'd in relevant part, rev'd in part*, 100 F.3d 1150, 1159 (4th Cir. 1996).

Co.,[231] that "[d]ifferential diagnosis is a reliable basis to prove general causation in this circuit"[232] and that "according to the Second Circuit, if a qualified expert performs a reliable differential diagnosis, the plaintiff need not satisfy the general causation requirement."[233] But the view that differential diagnosis necessarily is sufficient to establish general causation is not borne out by *McCullock*. The Circuit there merely registered its approval of the expert's reliance on a variety of sources to arrive at an opinion as to causation in one patient's case, an opinion that, so far as the Circuit's opinion indicated, did not differentiate between general and specific causation. It is not at all clear that the Court regarded differential diagnosis as inevitably probative of general causation.[234]

The plaintiffs point out that researchers and clinicians in the field of liver toxicology use a variety of data and analysis – sometimes including differential diagnoses on individual patients – to conclude that a particular drug is capable of causing a particular injury.[235] The plaintiffs further point out, correctly, that the physicians who first determined that Rezulin caused certain types of liver injuries (non-silent ones) had no published studies but made judgments based on a totality of information.[236] The implication is that physicians retained for this litigation should be able to testify that Rezulin is a possible, and the most likely, cause of particular plaintiffs' symptoms – symptoms

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231 *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038 (2d Cir. 1995).

232 *Perkins v. Origin Medsystems, Inc.*, 299 F. Supp. 2d 45, 57 (D. Conn. 2004).

233 *Plourde v. Gladstone*, 190 F. Supp. 2d 708, 722 n.7 (D. Vt. 2002).

234 *See* 61 F.3d at 1043-44.

235 Pl. Facts ¶¶ 8-22; Tr. 5/21/03, at 234-43 (Julie direct).

236 Pl. Facts ¶¶ 5, 10, 16.

that were consistent with liver injury but that occurred without elevated enzymes – and that these physicians should be able to do so by relying upon, among other things, the expert testimony that the defendants are seeking to exclude on this motion.

The plaintiffs' mistake throughout is to overlook the fact that science and medicine refine themselves over time, gradually converting tentative hypotheses into reliable principles. The idea that Rezulin sometimes causes acute liver injury, albeit not silently, appears not now to be controversial for a number of reasons, including the existence of a significant number of compelling case reports and several generally accepted, empirically verified (though not necessarily perfectly understood) physiological processes through which drug-induced liver injury occurs. A medical theory that has no little or no empirical support, is entirely unaccepted outside the very lawsuit in which the theory is being advanced for the first time, and that suffers from numerous analytical gaps is an entirely different matter.

VIII. Conclusion

To sum up, the plaintiffs have not established the reliability of the silent injury theory. The theory never has been tested or peer-reviewed, has not been published except by Dr. Smith after the commencement of this litigation and only then in speculative terms and suspicious circumstances, and has no acceptance outside this litigation. The plaintiffs' experts have ignored information that appears to call crucial aspects of their theory into question. The theory rests on a series of empirically unbridgeable analytical gaps. Most importantly, the experts have not established a sound basis for concluding that Rezulin-induced apoptosis can occur at clinically significant levels and remain silent. Similarly, the experts have failed to show that any mitochondrial changes attributable to Rezulin themselves can cause apoptosis or that any cholestatic injury due to Rezulin's

effect on the BSEP would be silent.

Thus, all the experts really have are a set of studies in which Rezulin produced apoptosis in tissue cultures. These studies, however, do not "fit" the opinion they are used to support. Save one study on rat hepatocytes, all were performed on cancerous liver cells and cancerous or otherwise unhealthy cells of other organs. The plaintiffs' counsel and their experts have acknowledged that studies on such cells are not reliable predictors of *in vivo* outcomes in a non-cancerous liver.

Nor is the study on rat hepatocytes a reliable basis for extrapolation. Among other issues, there is no reason to believe that the doses used in that study (or, for that matter, in many of the other studies presented to the Court) approximated the doses to which clinically relevant quantities of cells in the human liver are exposed.

The plaintiffs attempt to deal with all of these problems by arguing that the testimony in question could factor into the diagnosis of an individual patient. The plaintiffs' position is that a physician, faced with a patient who took Rezulin and had symptoms of liver disease but no elevated enzymes, could use the opinions of Drs. Smith and Reed and the research they cite to conclude that the patient's injury was caused by Rezulin. The flaw, however, is that a physician must have some reliable basis for believing that a particular substance is capable of causing the injury in question in relevant circumstances before concluding that the substance caused that injury in a particular case. Here, there is no such basis.

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In a now-famous passage, the Supreme Court recognized that the trial judge's gatekeeping role:

Appendix: Scientific and Medical Studies Discussed in the Opinion

Myung-Ae Bae & Byoung J. Song, *Critical Role of c-Jun N-Terminal Protein Kinase Activation in Troglitazone-Induced Apoptosis of Human HepG2 Hepatoma Cells*, 63 MOLECULAR PHARMACOL. 401 (2003) (Ex. 10).	Bae & Song (2003)
D. Montgomery Bissell et al., *Drug-Induced Liver Injury: Mechanisms and Test Systems*, 33 HEPATOL. 1009 (2001) (Ex. 17).	Bissell et al. (2001)
Rachel Butler et al., *Nonapoptotic Cell Death Associated with S-Phase Arrest of Prostate Cancer Cells via the Peroxisome Proliferator-Activated Receptor g Ligand, 15-Deoxy-D-^{12,14}-prostaglandin J_2*, 11 CELL GROWTH & DIFFERENTIATION 49 (2000) (Ex. 26).	Butler et al. (2000)
Stephen H. Caldwell et al., *A Pilot Study of a Thiazolidinedione, Troglitazone, in Nonalcoholic Steatohepatitis*, 96 AM. J. GASTROENTEROL. 519 (2001) (Ex. 27).	Caldwell et al. (2001a)
Stephen H. Caldwell, Letter to the Editor, *Efficacy and Safety of Troglitazone for Lipodystrophy Syndromes*, 134 ANNALS INTERNAL MED. 1008 (2001) (Ex. 31).	Caldwell (2001b)
Elena Elstner et al., *Ligands for Peroxisome Proliferator-Activated Receptor g and Retinoic Acid Receptor Inhibit Growth and Induce Apoptosis of Human Breast Cancer Cells* In Vitro *and in BNX Mice*, 95 PROC. NAT'L ACAD. SCI. 8806 (1998) (Ex. 49).	Elstner et al. (1998)
William A. Faubion et al., *Toxic Bile Salts Induce Rodent Hepatocyte Apoptosis via Direct Activation of Fas*, 103 J. CLINICAL INVESTIG. 137 (1999) (Ex. 58).	Faubion et al. (1999)
Miya Fukano et al., *Subacute Hepatic Failure Associated with a New Antidiabetic Agent, Troglitazone: A Case Report with Autopsy Examination*, 31 HUMAN PATHOL. 250 (2000) (Ex. 65).	Fukano et al. (2000)
Christoph Funk et al., *Cholestatic Potential of Troglitazone as a Possible Factor Contributing to Troglitazone-Induced Hepatotoxicity:* In Vivo *and* In Vitro *Interaction at the Canalicular Bile Salt Export Pump (Bsep) in the Rat*, 59 MOLECULAR PHARMACOL. 627 (2001) (Ex. 67).	Funk et al. (2001a)
Christoph Funk et al., *Troglitazone-Induced Intrahepatic Cholestasis by an Interference with the Hepatobiliary Export of Bile Acids in Male and Female Rats*, 167 TOXICOL. 83 (2001) (Ex. 68).	Funk et al. (2001b)
Ioanna Gouni-Berthold et al., *Troglitazone and Rosiglitazone Induce Apoptosis of Vascular Smooth Muscle Cells Through an Extracellular Signal-Regulated Kinase-Independent Pathway*, 363 NAUNYN-SCHMIEDEBERG'S ARCH. PHARMACOL. 215 (2001) (Ex. 78).	Gouni-Berthold et al. (2001)
You-Fei Guan et al., *Expression of Peroxisome Proliferator-Activated Receptor (PPARg) in Human Transitional Bladder Cancer and Its Role in Inducing Cell Death*, 1 NEOPLASIA 330 (1999) (Ex. 84).	Guan et al. (1999)

Sarah G. Harris & Richard P. Phipps, *Prostaglandin D_2,, Its Metabolite 15-d-PGJ_2,, and Peroxisome Proliferator Activated Receptor-ɣ Agonists Induce Apoptosis in Transformed, but Not Normal, Human T Lineage Cells*, 105 IMMUNOL. 23 (2002) (Ex. 85).	Harris & Phipps (2002)
Jeffrey R. Haskins et al., *Thiazolidinedione Toxicity to Isolated Hepatocytes Revealed by Coherent Multiprobe Fluorescence Microscopy and Correlated with Multiparameter Flow Cytometry of Peripheral Leukocytes*, 75 ARCH. TOXICOL. 425 (2001) (Ex. 87).	Haskins et al. (2001)
Steven K. Herrine & Cuckoo Choudhary, Letter to the Editor, *Severe Hepatotoxicity Associated with Troglitazone*, 130 ANNALS INTERNAL MED. 163 (1999) (Ex. 91).	Herrine & Choudhary (1999)
Takashi Izumi et al., *Prediction of the Human Pharmacokinetics of Troglitazone, a New and Extensively Metabolized Antidiabetic Agent, after Oral Administration, with an Animal Scale-up Approach*, 277 J. PHARMACOL. & EXP. THERAPEUTICS 1630 (1996) (Ex. 98).	Izumi et al. (1996)
Hartmut Jaeschke et al., *Forum: Mechanisms of Hepatotoxicity*, 65 TOXICOL. SCI. 166 (2002) (Ex. 100).	Jaeschke et al. (2002)
Yutaka Kawahito et al., *15-deoxy-$\Delta^{12,14}$-PGJ_2 Induces Synoviocyte Apoptosis and Suppresses Adjuvant-Induced Arthritis in Rats*, 106 J. CLINICAL INVESTIG. 189 (2000) (Ex. 108).	Kawahito et al. (2000)
Kenji Kawai et al., *Disposition and Metabolism of the New Oral Antidiabetic Drug Troglitazone in Rats, Mice and Dogs*, 47 ARZNEIM.-FORSCH./DRUG RES. 356 (1997) (Ex. 109).	Kawai et al. (1997)
Jae-Sung Kim et al., *Mitochondrial Permeability Transition in the Switch from Necrotic to Apoptotic Cell Death in Ischemic Rat Hepatocytes*, 124 GASTROENTEROL. 494 (2003) (Ex. 114).	Kim et al. (2003)
Youngsoo Kim, Nanjoo Suh, Michael Sporn & John C. Reed, *An Inducible Pathway for Degradation of FLIP Protein Sensitizes Tumor Cells to TRAIL-Induced Apoptosis*, 277 J. BIOL. CHEMISTRY 22320 (2002) (Ex. 115).	Kim et al. (2002)
Hironori Koga et al., *Involvement of $p21^{WAF1/Cipl}$, $p27^{Kipl}$, and $p18^{INK4c}$ in Troglitazone-Induced Cell-Cycle Arrest in Human Hepatoma Cell Lines*, 33 HEPATOL. 1087 (2001) (Ex. 117).	Koga et al. (2001)
James Kohlroser et al., *Hepatotoxicity Due to Troglitazone: Report of Two Cases and Review of Adverse Events Reported to the United States Food and Drug Administration*, 95 AM. J. GASTROENTEROL. 272 (2000) (Ex. 118).	Kohlroser et al. (2000)
Vsevolod E. Kostrubsky et al., *The Role of Conjugation in Hepatotoxicity of Troglitazone in Human and Porcine Hepatocyte Cultures*, 28 DRUG METABOLISM & DISPOSITION 1192 (2000) (Ex. 119).	Kostrubsky et al. (2000)

Tetsuya Kubota et al., *Ligand for Peroxisome Proliferator-Activated Receptor g (Troglitazone) Has Potent Antitumor Effect Against Human Prostate Cancer Both* In Vitro *and* In Vivo, 58 CANCER RES. 3344 (1998) (Ex. 120).	Kubota et al. (1998)
Paul Kwo et al., *Nuclear Serine Protease Activity Contributes o Bile Acid-Induced Apoptosis In Hepatocytes*, 268 AM. J. PHYSIOL. G613 (1995) (Ex. 123).	Kwo et al. (1995)
John J. Lemasters, *Mechanisms of Hepatic Toxicity V. Necrapoptosis and the Mitochondrial Permeability Transition: Shared Pathways to Necrosis and Apoptosis*, 276 AM. J. PHYSIOL.–GASTROINTESTINAL & LIVER PHYSIOL. G1 (1999) (Ex. 128).	Lemasters (1999)
John J. Lemasters et al., *The Mitochondrial Permeability Transition in Cell Death: A Common Mechanism In Necrosis, Apoptosis and Autophagy*, 1366 BIOCHIMICA ET BIOPHYSICA ACTA 177 (1998) (Ex. 127).	Lemasters et al. (1998)
Cho-Ming Loi et al., *Steady-State Pharmacokinetics and Dose Proportionality of Troglitazone and Its Metabolites*, 39 J. CLINICAL PHARMACOL. 920 (1999) (Ex. 137).	Loi et al. (1999a)
Cho-Ming Loi et al., *Clinical Pharmacokinetics of Troglitazone*, 37 CLINICAL PHARMACOKINETICS 91 (1999) (Ex. 136).	Loi et al. (1999b)
Hideyuki Miyoshi et al., *Hepatocyte Apoptosis After Bile Duct Ligation in the Mouse Involves Fas*, 117 GASTROENTEROL. 669 (1999) (Ex. 154).	Miyoshi et al. (1999)
Elisabetta Mueller et al., *Effects of Ligand Activation of Peroxisome Proliferator-Activated Receptor g in Human Prostate Cancer*, 97 PROC. NAT'L ACAD. SCI. 10990 (2000) (Ex. 156).	Mueller et al. (2000)
Elizabeth J. Murphy et al., *Troglitazone-Induced Fulminant Hepatic Failure*, 45 DIGESTIVE DISEASES & SCI. 549 (2000) (Ex. 158).	Murphy et al. (2000)
Kazuyasu Ohta et al., *Ligands for Peroxisome Proliferator-Activated Receptor g Inhibit Growth and Induce Apoptosis of Human Papillary Thyroid Carcinoma Cells*, 86 J. CLINICAL ENDOCRINOL. & METABOLISM 2170 (2001) (Ex. 162).	Ohta et al. (2001)
Takafumi Okura et al., *Troglitazone Induces Apoptosis via the p53 and Gadd45 Pathway in Vascular Smooth Muscle Cells*, 407 EUR. J. PHARMACOL. 227 (2000) (Ex. 163).	Okura et al. (2000)
Tushar Patel et al., *Apoptosis and the Liver: A Mechanism of Disease, Growth Regulation, and Carcinogenesis*, 30 HEPATOL. 811 (1999) (Ex. 166).	Patel et al. (1999)
Kurt Preininger et al., *Acute Troglitazone Action in Isolated Perfused Rat Liver*, 126 BRITISH J. PHARMACOL. 372 (1999) (Ex. 175).	Preininger et al. (1999)
Vinod Ramachandran et al., *Troglitazone Increases Cytochrome P-450 3A Protein and Activity in Primary Cultures of Human Hepatocytes*, 27 DRUG METABOLISM & DISPOSITION 1194 (1999) (Ex. 178).	Ramachandran et al. (1999)
Luigi Ravagnan et al., *Mitochondria, the Killer Organelles and Their Weapons*, 192 J. CELLULAR PHYSIOL. 131 (2002) (Ex. 181).	Ravagnan et al. (2002)

Robert Routh et al., *Troglitazone Inhibits Glutamine Metabolism in Rat Mesangial Cells*, 282 AM. J. PHYSIOL.–ENDOCRINOL. & METABOLISM E231 (2002) (Ex. 185).	Routh et al. (2002)
Brad H. Rovin et al., *15-Deoxy-D^{12,14}-prostaglandin J_2 Regulates Mesangial Cell Proliferation and Death*, 61 KIDNEY INT'L 1293 (2002) (Ex. 186).	Rovin et al. (2002)
J. Sahi et al., *Effect of Troglitazone on Cytochrome P450 Enzymes in Primary Cultures of Human and Rat Hepatocytes*, 30 XENOBIOTICA 273 (2000) (Ex. 187).	Sahi et al. (2000)
H. Sato et al., *Expression of Peroxisome Proliferator-Activated Receptor (PPAR)g in Gastric Cancer and Inhibitory Effects of PPARg Agonists*, 83 BRITISH J. CANCER 1394 (2000) (Ex. 188).	Sato et al. (2000)
Shoichiro Shishido et al., *Hydrogen Peroxide Overproduction in Megamitochondria of Troglitazone-Treated Human Hepatocytes*, 37 HEPATOL. 136 (2003) (Ex. 198).	Shishido et al. (2003)
S.S. Smaili et al., *Bax Translocation to Mitochondria Subsequent to a Rapid Loss of Mitochondrial Membrane Potential*, 8 CELL DEATH & DIFFERENTIATION 909 (2001) (Ex. 201).	Smaili et al. (2001)
Thomas Sodeman et al., *Bile Salts Mediate Hepatocyte Apoptosis by Increasing Cell Surface Trafficking of Fas*, 278 AM. J. PHYSIOL.–GASTROINTESTINAL & LIVER PHYSIOL. G992 (2000) (Ex. 206).	Sodeman et al. (2000)
Nobuhiko Takahashi et al., *Activation of PPARg Inhibits Cell Growth and Induces Apoptosis in Human Gastric Cancer Cells*, 455 FEBS LETTERS 135 (1999) (Ex. 211).	Takahashi et al. (1999)
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Mark A. Tirmenstein et al., *Effects of Troglitazone on HepG2 Viability and Mitochondrial Function*, 69 TOXICOL. SCI. 131 (2002) (Ex. 218).	Tirmenstein et al. (2002)
M. Toyoda et al., A *Ligand for Peroxisome Proliferator Activated Receptor g Inhibits Cell Growth and Induces Apoptosis in Human Liver Cancer Cells*, 50 GUT 563 (2002) (Ex. 220).	Toyoda et al. (2002)
Y. Toyoda et al., *Toxic Effect of Troglitazone on Cultured Rat Hepatocytes*, 68 LIFE SCI. 1867 (2001) (Ex. 221).	Toyoda et al. (2001)
Yasunori Tsubouchi et al., *Inhibition of Human Lung Cancer Cell Growth by the Peroxisome Proliferator-Activated Receptor-g Agonists Through Induction of Apoptosis*, 270 BIOCHEM. AND BIOPHYS. RES. COMMUNICATIONS 400 (2000) (Ex. 224).	Tsubouchi et al. (2000)
Yui Yamamoto et al., *Cytotoxicity and Apoptosis Produced by Troglitazone in Human Hepatoma Cells*, 70 LIFE SCI. 471 (2001) (Ex. 239).	Yamamoto et al. (2001)

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Kaname Yoshizawa et al., *Peroxisome Proliferator-Activated Receptor ɡ Ligand Troglitazone Induces Cell Cycle Arrest and Apoptosis of Hepatocellular Carcinoma Cell Lines*, 95 CANCER 2243 (2002) (Ex. 243).	Yoshizawa et al. (2002)